DOCUMENT RESUME

ED 214 658	PS 012 759
TITLE	Effects of Prescription Drugs During Pregnancy. Hearing Before the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, U.S. House of Representatives, Ninety-Seventh Congress, First Session (July, 30, 1981).
INSTITUTION	Congress of the U.S., Washington, D.C. House Committee on Science and Technology.
PUB DATE	30 Jul 81
NOTE	248p.; Some pages may be marginally legible due to small print size.
EDRS PRICE	MF01/PC10 Plus Postage.
DESCRIPTORS	Accountability; *Drug Use; Ethics; Guidelines; *Information Needs; Legislation; Medical Evaluation; Mothers; Neonates; Neurological Impairments; *Perinatal Influences; Pharmacology; *Policy Formation; *Pregnancy; Public Policy; *Research Needs; Safety
IDENTIFIERS	Epidemiology; Food and Drug Administration; Informed Consent; Patients Rights; Public Safety; *Teratology

ABSTRACT

This hearing focuses on scientific and policy deficiencies in the area of drug-induced birth defects. Witnesses charge that (1) the Food and Drug Administration (FDA) does not require the kinds of clinical studies that are necessary to actually determine the safety of drugs used in pregnancy, (2) the FDA does nothing to enable women to find out about the effects of drugs during pregnancy even when such information could easily be made available, (3) the FDA does not do the kind of followup epidemiological studies that are necessary to clearly determine the safety of drugs in pregnancy, (4) the FDA's system for retrieving drug information on adverse effects is poor and this in turn obviously influences the quality of epidemiology, (5) labeling for physicians is not current, is often evasive, and is not based upon the best information available, (6) the majority of drugs given to pregnant women are not really approved by the FDA as safe for this use, and (7) most people, and particularly pregnant women, are not aware that the drug approval process is a "risk/benefit" process that limits the use of drugs that are not "safe" in the dictionary sense of the word. In addition to testimony related to these charges, teratological animal testing, epidemiological studies, bioethical issues, and the issue of informed consent are discussed. Numerous related documents are included in the record (RH)

****
* Reproductions supplied by EDRS are the best that can be made *
* from the original document. *
****

PS

EFFECTS OF PRESCRIPTION DRUGS DURING PREGNANCY

ED214658

U.S. DEPARTMENT OF EDUCATION
NATIONAL INSTITUTE OF EDUCATION
EDUCATIONAL RESOURCES INFORMATION CENTER (ERIC)

☒ This document has been reproduced as received from the person or organization originating it.

☐ Minor changes have been made to improve reproduction quality.

- Points of view or opinions stated in this document do not necessarily represent official NIE position or policy.

HEARING

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

OF THE

COMMITTEE ON SCIENCE AND TECHNOLOGY U.S. HOUSE OF REPRESENTATIVES

NINETY-SEVENTH CONGRESS

FIRST SESSION

JULY 30, 1981

[No. 62]

Printed for the use of the
Committee on Science and Technology

PS 012759

85-762 O

U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON : 1981

COMMITTEE ON SCIENCE AND TECHNOLOGY

DON FUQUA, Florida, *Chairman*

ROBERT A. ROE, New Jersey
GEORGE E. BROWN, Jr., California
JAMES H. SCHEUER, New York
RICHARD L. OTTINGER, New York
TOM HARKIN, Iowa
MARILYN LLOYD BOUQUARD, Tennessee
JAMES J. BLANCHARD, Michigan
TIMOTHY E. WIRTH, Colorado*
DOUG WALGREN, Pennsylvania
RONNIE G. FLIPPO, Alabama
DAN GLICKMAN, Kansas
ALBERT GORE, Jr., Tennessee
ROBERT A. YOUNG, Missouri
RICHARD C. WHITE, Texas
HAROLD L. VOLKMER, Missouri
HOWARD WOLPE, Michigan
BILL NELSON, Florida
BERYL ANTHONY, Jr., Arkansas*
STANLEY N. LUNDINE, New York
ALLEN E. ERTEL, Pennsylvania
BOB SHAMANSKY, Ohio
RALPH M. HALL, Texas
DAVE McCURDY, Oklahoma
MERVYN M. DYMALLY, California

LARRY WINN, Jr., Kansas
BARRY M. GOLDWATER, Jr., California
HAMILTON FISH, Jr., New York
MANUEL LUJAN, Jr., New Mexico
HAROLD C. HOLLENBECK, New Jersey
ROBERT S. WALKER, Pennsylvania
EDWIN B. FORSYTHE, New Jersey
WILLIAM CARNEY, New York
MARGARET M. HECKLER, Massachusetts
F. JAMES SENSENBRENNER, Jr., Wisconsin
VIN WEBER, Minnesota
JUDD GREGG, New Hampshire
RAYMOND J. McGRATH, New York
JOE SKEEN, New Mexico
CLAUDINE SCHNEIDER, Rhode Island
JIM DUNN, Michigan
BILL LOWERY, California

Harold P. Hanson, *Executive Director*
Philip B. Yeager, *General Counsel*
Regina A. Davis, *Administrator*
Gerald E. Jenks, *Minority Staff Director*

Subcommittee on Investigations and Oversight

ALBERT GORE, Jr., Tennessee, *Chairman*

BOB SHAMANSKY, Ohio
HAROLD L. VOLKMER, Missouri

ROBERT S. WALKER, Pennsylvania
MANUEL LUJAN, Jr., New Mexico

Thomas P. Grumbly, *Staff Director*
David D. Clement, *Minority Counsel*

---

*On assignment to Budget Committee for 97th Congress.

CONTENTS

WITNESSES

Page

July 30, 1981:

Doris Haire, president, National Women's Health Network 5

Jonathan Bingham, a Representative in Congress from the State of New York 128

Dr. Kenneth Ryan, chairman, Department of Obstetrics and Gynecology, Harvard Medical School and Dr. Yvonne Brackbill, professor of psychology, University of Florida 149

Dr. Phillip Goldstein, chairman, Department of Obstetrics and Gynecology, Johns Hopkins University Medical School, Baltimore, Md.; Dr. Sanford Cohen, chairman, Department of Pediatrics, Wayne State University, Detroit, Mich.; and Dr. Sumner Yaffe, professor of pediatrics and pharmacology, Childrens' Hospital, Philadelphia, Pa 174

Dr. Dennis Slone, codirector, Drug Epidemiology Unit, School of Public Health, Boston University Medical Center 196

Hon. Arthur Hull Hayes, Jr., M.D., Commissioner, Food and Drug Administration; accompanied by Marion J. Finkel, M.D., Associate Director for New Drug Evaluation, Bureau of Drugs, FDA; Judith K. Jones, M.D., Ph. D., Director, Division of Drug Experience, Bureau of Drugs, FDA; and Tom Scarlett, Chief Counsel 209

EFFECTS OF PRESCRIPTION DRUGS DURING PREGNANCY

THURSDAY, JULY 30, 1981

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
Washington, D.C.

The subcommittee met, pursuant to call, at 9 a.m., in room 2318 of the Rayburn House Office Building, Hon. Albert Gore (chairman of the subcommittee) presiding.

Mr. Gore. The subcommittee will come to order. Childbirth is one of those special, miraculous events in life. For those who have witnessed it, beauty of the experience is moving almost beyond words.

And yet, too often in the midst of this joy, lies the profound tragedy of birth defects. Over 100,000 babies are born in this country every year with significant malformations, defects, and neurological deficits. The health costs of this deep human tragedy are enormous, and the emotional damage is beyond calculation.

While we do not yet know the causes of many of these malformations and problems, we do know—from painful experience—that the use of some drugs before and particularly during pregnancy can cause birth defects. In 1962, thalidomide became a household word around the world. Thousands of babies were born with deformed limbs because their mothers took a drug designed to help them through their pregnancies. The United States was fortunately spared the agony of this experience, through the combination of good luck and good work on the part of the FDA. Nevertheless, the thalidomide experience shocked the United States into enacting the toughest and most thorough drug laws in the world.

It is ironic then and sad, that 19 years later we need to be in a committee room discussing our scientific and policy deficiencies in the area of drug-induced birth defects. It is undeniable, however, that we have not made the same kind of major scientific progress in this area that we have with other conditions and diseases. Some of that delay is due to lack of research funds, some is due to the toughness of the problems, and some, perhaps, to the unwillingness of public agencies and private businesses to look the issues straight in the eye.

Today, the subcommittee will hear a variety of perspectives on the subject of drug-induced birth defects and malformations. We will try to evaluate charges by some of our witnesses that:

FDA does not require the kinds of clinical studies that are necessary to actually determine the safety of drugs used in pregnancy.

FDA does nothing to enable women to find out about the effects of drugs during pregnancy even when such information could easily be made available.

FDA does not do the kind of followup epidemiology studies that are necessary to clearly determine the safety of drugs in pregnancy.

FDA's system for retrieving drug information on adverse effects is poor and that this obviously influences the quality of epidemiology.

Labeling for physicians is not current, is often evasive, and is not based upon the best information available.

The majority of drugs given to pregnant women are not really approved by the FDA as safe for this use.

Most people, and particularly pregnant women are not aware that the drug approval process is a "risk/benefit" process that limits the use of drugs that are not "safe" in the dictionary sense of the word.

In order to examine these criticisms in a careful way, the subcommittee will want to discuss the state of the art in animal testing that forms the basis for the science of teratology, problems and possibilities in the emerging science of epidemiology that offer hope for better drug information in the future, bioethical issues that continue to constrain us in experimentation and research design, and problems that surround the issue of insuring the informed consent of both mothers and their unborn children. In the area of informed consent, I will be particularly anxious to hear what the FDA intends to do about patient package inserts. While they may not be universally applicable to all drugs, I am struck in this area by the good they could do in helping mothers make informed choices about which drugs to inflict upon their unborn children.

I want to make it clear that our focus here today is constructive. The subcommittee is interested in seeing what kinds of research and policy advances are possible, and what kinds of resources are needed by the FDA and industry to make those advances. It is inevitable that discussion about specific drugs will arise as we attempt to evaluate the issue. We are not in the business here of unduly concerning people. But if we are to do our job, we must examine specific cases that are troublesome in order to illustrate general principles.

As a society, we have no greater responsibility than to care for the next generation. In the research and regulatory environment surrounding drug effects and pregnancy, this responsibility may mean that we need to give the unborn child a greater "benefit of the doubt" than we have in the past.

I would like to ask unanimous consent that at this point in the record the statement of the ranking minority member, Mr. Walker, be included and he will have an opportunity to present that when he arrives. He was unavoidably detained.

[The opening statement of Representative Robert Walker follows:]

PREPARED STATEMENT OF ROBERT WALKER

Thank you, Mr. Chairman. Our hearing today is of particular importance to me because before I came to Congress I was trained to be an educator. Today my wife still works with the youth in our schools at home. The children of this great nation are our priceless future. Despite all of man's efforts to achieve immortality the truth remains that our children are our one fragile thread toward the uncertain future.

The human race has been the recipient of uncalculable benefits from the chemical revolution starting about the time of the Second World War. In this country we have become used to accepting without question a belief that each new product would give us fantastic benefits without hidden costs.

But we are learning that we were wrong. In recent years we have learned that the fragile human gene train is at far greater hazard from synthetic chemical compounds than we had suspected in the past.

I happen to believe that we have too much government. We suffer from too much regulation. We suffer from too much bureaucracy. But this is an area where government has a supreme duty to preserve and protect the public. We must do all necessary research. We must know not only what the benefits are, but we must also know what the risks are. And then we must let the public know that information.

If the evidence today indicates that we have not done that research; that we have not determined the risks; or that we have not made the information available—then government has failed the public.

It is not often that I quote Thomas Jefferson, but he was correct when he said "That government is best which governs least." But there is a legitimate function of government in protecting the innocent public, and none are so innocent as the unborn.

Life is not without risks. Safety is a relative concept. Virtually everything we do carries some element of risk involved. Each of us builds a body of experience upon which we routinely make risk analysis in our day-to-day decisions. But the average American has insufficient experience with drugs and medical procedures to weigh the risks against the benefits which are anticipated. We must depend on the information we are given by others.

We fund billions in research and development. We routinely over-regulate in dozens of areas. The charges that we, as a society, may place the unborn at risk are difficult to understand, but if they are true they will merit the immediate action of this committee to see that they are corrected at once.

Mr. GORE. I would like to call on our ranking majority member, Mr. Shamansky.

Mr. SHAMANSKY. Thank you, Mr. Chairman. No one has ever been given a more pleasant task than I have at this moment, which is to introduce our first witness, Doris Haire. Doris Haire is president of the American Foundation for Maternal and Child Health, a foundation established by her and her husband John. I must say that John and I first met 34 years ago when we sat down next to each other during our first day at Harvard Law School. He has had a distinguished career and is now president of the Council on Financial Aid to Education after having been one of the youngest vice presidents of the New York Stock Exchange, et cetera. Interestingly enough, Doris Haire has pursued her own career in the area of maternal and child health in addition to raising three handsome children. I think it is significant that the Haires know what it means to lose a child because of a congenital birth defect. I think that Doris and John have done magnificent work. They have gained recognition nationally. I have seen Doris on the "Today" program, among others. I am delighted to welcome friends of 34 years here. Thank you, Mr. Chairman.

Mr. GORE. Thank you. Before we hear from you, Mrs. Haire, I want to welcome the chairman of the Science, Research and Technology subcommittee of this full committee who has had a personal interest in these issues and invite him to join us in this hearing today, and recognize him at this time for any statement.

Mr. WALGREN. Thank you, Mr. Chairman. I appreciate the opportunity to sit with you and learn about these issues along with this committee. I think you are doing a tremendous service in bringing the parties that will be witnesses before these hearings together so we can all talk in public about the problems that concern us all and that we all seek solutions for.

Although I am not a member of this committee I am particularly grateful to be able to participate in this hearing with you. As you indicated I do chair the Science and Research Subcommittee of the Committee on Science and Technology and I am also a member of the Health Subcommittee. Through that interest I have had an ongoing interest in the importance of carefully monitoring medical drug use in our country. Also as a new father I especially have been struck in these last 9 months with what it means to have a healthy newborn child and in looking back on my experience on the subcommittee I do believe there is more that we can do as a Government to guarantee the health and well being of future generations.

Sadly the consequences of improper drug use during pregnancies do have a catastrophic effect and not just on the mother but on the newborn child. The Food and Drug Administration often assures us they are monitoring all approved prescription drugs which can be taken during pregnancy but I think we have to ask whether the FDA is properly focusing on the impact of the drugs on the fetus itself. The unborn child is at the most vulnerable part of our population and injuries to that child during that time period are forever. For over a year I have been talking with FDA about handling a particular drug called Bendectin. I think it will be helpful to talk again with the FDA about how they are monitoring the performance with the drugs so that we are sure the proper situation prevails. Bendectin is an antinausea drug prescribed to ease morning sickness in pregnant women and it is widely taken. However for some time a number of physicians have suggested Bendectin may—and there is an uncertainty there—but may cause birth defects. Last September the FDA's own Maternal Health Advisory Committee concluded there was indeed a residual uncertainty about whether Bendectin caused birth defects and the committee at that time—this was a committee of physicians—recommended a strong patient package insert as a warning so that mothers could evaluate this question for themselves. The FDA started to draft a warning which pregnant women could read for themselves but earlier this year the administration halted the FDA's efforts. They did this in the process of a blanket freeze on all proposed regulations the good regulations as well as the bad regulations. I am concerned that this administration through that inaction is sabotaging efforts to warn women about the potential danger of this drug and other drugs that may properly have patient package inserts. No one can say and I do not know for certain whether Bendectin causes birth defects. The experts cannot agree on that but under those circumstances the least we can do is guarantee the doubts about this drug are effectively communicated to pregnant women so they can knowingly make up their minds about that risk. It is now 1 year after that recommendation came from the Maternal Health Advisory Committee and still we have no patient package insert. I look forward to talking with the representatives of FDA and hopefully through this hearing we will get the kinds of mutual communication with the public that will incline our system in the right direction. I appreciate the opportunity to join you, Mr. Chairman.

Mr. **Gore**. Thank you very much.

We would like to call now on our first witness, Mrs. Doris Haire, who is accompanied by her husband. We welcome you both and without objection the entire text of your written statement will be put in the record and we invite you to proceed with the presentation of as much or all of it as you see fit.

STATEMENT OF DORIS HAIRE, PRESIDENT, NATIONAL WOMEN'S HEALTH NETWORK

Ms. **Haire**. I would like to thank you for this opportunity. It is a privilege and most timely.

For more than a decade I have questioned the wisdom of the U.S. Food and Drug Administration's procedures and policies in regard to how that agency evaluates and regulates the safety of drugs, especially those drugs used in pregnancy and obstetrics. In my report to the National Women's Health Network, entitled "How the FDA Determines the 'Safety' of Drugs—Just How Safe Is 'Safe'?" which I submit for the record, I describe my findings. I prepared the report as much for the Commissioner of the FDA as for the National Women's Health Network. I became convinced of the need for such a report by the resistance I encountered from various officials in the Bureau of Drugs not all but many as I questioned them regarding the FDA's evaluation of drugs, and, in particular, obstetric drugs. It became obvious that the FDA's inadequacies in this regard would not be brought to the Commissioner's attention by those responsible for those inadequacies. In keeping with my intent I sent a copy of each successive draft of my report to Dr. Jere Goyan, former Commissioner of the FDA at that time. I repeatedly told Dr. Goyan and other FDA officers that I would correct any inaccuracies in my report which the FDA could document as errors. No such documentation was offered.

[The report mentioned above follows:]

How the FDA Determines the "Safety" of Drugs — Just How Safe Is "Safe"?

Most Americans do not realize what it means when a drug or medical device is designated as "safe" by the U. S. Food and Drug Administration (FDA), especially in cases where the drug is to be taken by or administered to a woman during pregnancy, labor, birth, and lactation. There is no drug, whether prescription drug or over-the-counter remedy, that is without risk. You owe it to yourself (and if pregnant, you owe it to your baby) to learn as much as possible about the drugs you take.

Many health professionals have not been taught how to distinguish an FDA-approved use of a drug from a non-approved use. Therefore, before you purchase or take a prescription drug you may wish to ask your doctor or pharmacist to let you read the package insert of that drug. If you are hospitalized and your doctor is not available, ask the hospital pharmacist to let you read the package insert. The package insert is the drug information leaflet written and supplied by the manufacturer and approved by the FDA. Although written for the physician, most consumers can understand the relevant sections (i.e., "Indications", "Contraindications", "Warnings", "Precautions", "Adverse Reactions", etc.).

Don't hesitate to question your doctor about the risks vs. the benefits of the drug he or she may prescribe for you. Your doctor is legally obligated to obtain your informed consent to treatment. This requires your doctor to inform you of the drug's known adverse effects, the "areas of uncertainty" regarding the drug's delayed, long-term effects, and the non-pharmacologic alternatives to the drug. Since your doctor may not be aware of the information in this pamphlet, you may wish to share with him or her the following information, which is presented in the form of answers to commonly asked questions about drug safety.

WHAT DOES "APPROVED AS SAFE BY THE FDA" REALLY MEAN?

- FDA DOES NOT GUARANTEE THE SAFETY OF FDA APPROVED DRUGS

FDA approval of a drug as safe does not automatically mean that the drug has been subjected to a properly controlled scientific evaluation and follow-up of individuals exposed to the direct and indirect effects of the drug. The Director of the FDA's Bureau of Drugs has confirmed in writing that the FDA does not guarantee the safety of any drug – not even those drugs which the FDA has officially approved as safe.

- DICTIONARY AND FDA DIFFER ON DEFINITION OF SAFE

When the FDA does use the term "safe" the agency does not use the definition, "free from harm or injury", which is found in every U. S. dictionary. To the FDA the term "safe" is a relative term, based on data on the known risks and what the FDA considers to be the potential risks and benefits of the particular drug.

HOW CAN ONE TELL IF THE FDA HAS APPROVED A DRUG AS SAFE FOR A PARTICULAR USE?

- ONLY THOSE USES OF A DRUG WHICH ARE MENTIONED IN THE "INDICATIONS" SECTION OF THE PACKAGE INSERT ARE FDA–APPROVED USES OF THE DRUG

The fact that a use of a drug is mentioned in a section of the package insert other than the "Indications" section does NOT, in itself, indicate FDA approval of that use. If, for example, the section of the package insert entitled "Usage in Pregnancy/Obstetrics" mentions the use of the drug during pregnancy, obstetrics (labor and delivery), or lactation but such uses are not mentioned in the "Indications" section, then the FDA has NOT approved the drug as safe for use in pregnancy, labor, delivery, or lactation.

HOW DOES THE FDA DETERMINE WHETHER A DRUG IS SAFE?

- FDA RELIES ON MANUFACTURER'S HONESTY REGARDING DRUG'S SAFETY

The FDA now requires the drug sponsor (manufacturer) to carry out animal studies (rats, mice, etc.) and three phases of human testing. However, the manufacturer's data on safety are usually accepted in good faith by the FDA. The FDA does not check all data to make sure the data submitted are not inaccurate or fraudulent unless there is reason for the agency to believe otherwise.

- DATA ON SAFETY WITHHELD FROM PUBLIC SCRUTINY

The FDA does not allow concerned consumer groups or responsible citizens to examine the design of the research study, or to check the accuracy of the manufacturer's data presented to the FDA. Without such examination it is almost impossible for concerned individuals or groups to effectively challenge the appropriateness of the study's design or the accuracy of the data before the drug is approved by the FDA.

© 1980, Doris Haire, Chair, Committee on Health Law and Regulation, National Women's Health Network, Washington, D.C.

- FDA ACCEPTS UNPUBLISHED DATA AS EVIDENCE OF DRUG SAFETY

Although the scientific community questions the validity of research data which have not been subjected to review by specialists with equal or greater knowledge before publication in a recognized medical journal, the FDA accepts unpublished data from the manufacturer as evidence of a drug's safety.

- DATA MAY BE BIASED DUE TO ECONOMIC PRESSURES

Data accepted by the FDA as evidence of a drug's safety may be prepared by researchers who are in the employ of or under contract to the manufacturer of the drug, or by researchers who are members of university departments receiving grants or gifts from the drug's manufacturer.

- COMBINATIONS OF SEPARATE DRUGS NOT REQUIRED TO BE TESTED FOR SAFETY

Only single drugs are evaluated for approval. Common combinations of separate drugs are not usually subjected to any review for adverse reactions by the FDA. Combinations which are known to be ineffective or unsafe, however, may sometimes be noted in the package insert.

- MANY DRUGS BYPASS FDA'S ADVISORY COMMITTEES

Many drugs approved as safe are allowed to bypass the deliberations of the outside experts who make up the FDA advisory committee responsible for the category of drugs under which the drugs in question fall. While the outside experts have been faulted for having a pro specialty bias, their participation in FDA deliberations broadens the base for decision-making.

- "ME TOO" DRUGS APPROVED WITHOUT ADEQUATE SCIENTIFIC EVALUATION

A drug may be approved as safe for a specific use merely because the drug is similar to a drug already on the market — even though the old drug was never subjected to a properly controlled scientific investigation or follow-up to determine its safety when used in general medicine, under non-research conditions.

WHO HAS ACCESS TO FDA DATA ON "SAFETY"?

- FDA DECLARES DATA ON SAFETY AS "TRADE SECRET"

Despite repeated objections by various federal investigative panels the FDA continues to classify as "trade secrets" the raw (basic) data on safety which the manufacturer presents in order to obtain the agency's approval of the drug. Such a classification makes the data unavailable to concerned groups which have reason to believe there may have been serious flaws in the design of the study on safety, including the possibility of deliberate exclusion of subjects who may have been adversely affected by the drug.

- PROPOSED NEW DRUG BILLS WOULD LEGALIZE FDA'S WITHHOLDING DATA ON SAFETY FROM THE PUBLIC

The FDA supports the proposed Drug Regulation Reform Act and similar bills which, if enacted, would classify the manufacturer's basic data on safety as a "trade secret" as a matter of law rather than FDA preference. If enacted, this bill would put the information permanently beyond public scrutiny.

WHO DETERMINES THE SAFETY OF DRUGS?

- MAKEUP OF FDA ADVISORY COMMITTEES SUGGESTS PROFESSIONAL BIAS IN DECISION-MAKING

Members of FDA advisory committees, who analyze the relative benefits and risks of a drug, are usually chosen from the ranks of the specialty which administers the category of drugs on which they are asked to deliberate. Seldom do the committees include a balance of experts who must deal with the adverse effects of the drugs under deliberation. For example, the FDA's Anesthetic and Life Support Drug Advisory Committee is made up almost exclusively of anesthesiologists. Neurologists and internists, who deal with some of the very serious adverse effects of surgical and obstetric anesthesia, are not included as members of that advisory committee.

- FDA RELUCTANT TO DIVULGE NAMES OF FDA OFFICERS RESPONSIBLE FOR APPROVING SPECIFIC DRUGS

The FDA remains unclear as to whether this information may be requested and obtained under the Freedom of Information Act. Requesting information through one's U. S. Senator or Representative is more likely to get results. (If you need the full name and address of your Senator or Representative, your local library or newspaper will provide you with that information.)

DOES THE FDA MAKE AN EFFORT TO DETERMINE IF THERE ARE DELAYED ADVERSE EFFECTS OF DRUGS?

- PUBLIC USED TO DETERMINE DELAYED ADVERSE EFFECTS OF DRUGS

The FDA does not require, as part of the approval process, that the manufacturer of the drug carry out a systematic, long-term follow-up of individuals exposed to the drug. Nor does the FDA have any system of periodic review of drug effects once the drug is on the market.

Negative or adverse effects of drugs may only appear after widespread use. The lack of follow-up to evaluate the effects on the child of drugs ingested or administered to the mother during pregnancy, childbirth, and breast-feeding is particularly irresponsible since no drug has been adequately tested for safety in regard to the exposed offspring.

- SYSTEM FOR COLLECTING DATA ON ADVERSE EFFECTS INADEQUATE

An investigation by the U. S. General Accounting Office (the federal "watchdog" agency) of the FDA's policies, procedures, and systems found a notable discrepancy between the data collected by the FDA's adverse reaction reporting system and that data which appeared in the published literature. In the case of one fetal effect, that effect appeared 20 times more often in the published literature than the incidence noted by the FDA. FDA explanations for the incomplete data include not putting research literature reports into the computer system and physician reluctance to report adverse drug reactions to the FDA.

- FDA RELIES ON MANUFACTURER FOR INFORMATION ON ADVERSE EFFECTS

In reviewing the safety of drugs already on the market, the FDA tends to rely on the manufacturer to keep the agency current in regard to the adverse effects of his products. Understandably, a manufacturer is not anxious to report adverse reactions to his product because of the possibility of loss of sales and of litigation resulting from drug-induced injury.

HOW DOES THE FDA HANDLE ADVERSE REACTION REPORTS?

- PHYSICIANS NOT REQUIRED TO REPORT ADVERSE DRUG REACTIONS TO FDA

The FDA has no legal authority to require physicians, nurses, or other health professionals to report adverse drug reactions to the FDA. Therefore, there is no way the FDA can determine the exact rate of adverse reactions to an FDA-approved drug when it is used in general medicine under non-research conditions.

- CHANGING AN ADVERSE REACTION "REPORT" TO AN "INQUIRY" REMOVES MANUFACTURER'S LEGAL OBLIGATION TO INFORM FDA

The FDA does require drug manufacturers to file with the FDA all adverse drug reaction reports received from physicians. However, the manufacturer can avoid filing such a report if the physician can be persuaded to change a report to an "Inquiry", which the manufacturer is not required to file with the FDA.

- FDA MAKES NO REAL EFFORT TO FACILITATE PUBLIC INQUIRY OR REPORTING OF ADVERSE REACTIONS

The FDA does not require the manufacturer to note in the drug's package insert the name and address of the FDA division responsible for evaluating the safety and effectiveness of the drug in order to facilitate reporting of an adverse drug reaction or a request for information by concerned consumers.

- FDA SELDOM FOLLOWS UP ON ADVERSE REACTION REPORT BY CONSUMERS

If a patient reports an adverse drug reaction to the FDA but the prescribing physician refuses to provide the FDA with the patient's medical records, the FDA will usually not follow up and investigate the consumer's report. To obtain a copy of your hospital medical records see "What You Can Do", page 8.

WHAT IF A PHYSICIAN USES A DRUG FOR A NON-APPROVED USE?

- PHYSICIAN IS FREE TO USE DRUG IN WAYS NOT APPROVED AS SAFE BY FDA

The FDA cannot prohibit a physician from using a drug for a use not approved by the FDA. However, in the event of drug-induced injury, the use of a drug not approved by the FDA may affect the court's decision should litigation arise.

CAN ONE TRUST THE INFORMATION IN THE "PACKAGE INSERT"?

- PACKAGE INSERT IS WRITTEN BY THE MANUFACTURER

In the majority of cases, the information in the package insert is written by the manufacturer. The text is then submitted to the FDA, and if deemed appropriate, the text is approved by the FDA. The result is that the text of many package inserts (especially those drugs used in obstetrics) appears to be purposely ambiguous when discussing the drug's known adverse effects, the inherent risks, and the relevant "areas of uncertainty" regarding the delayed, long-term effects of the drug on human development and neurologic functioning.

- INFORMATION IN INSERT IS RARELY CURRENT

Whether due to FDA inertia or pressure from the pharmaceutical industry, once information is known regarding a drug's adverse effects it may be years before that information appears in the package insert (if it appears at all).

FDA officers have publicly acknowledged that there is significant under-reporting of adverse drug reactions by physicians because of fear of litigation following such reports. Yet the FDA continues to rely on reports from physicians and manufacturers as the primary souces of information for the package insert. The FDA's other source of information is articles published in the medical journals, most of which appear a year or more after the research findings are known. Unfortunately, the authors of the articles tend to reflect the bias (and fear of litigation) shown by the medical specialty which sponsors or is served by the journal. In addition, many authors receive research grants and other remuneration from the very drug companies whose products they publish articles about.

- INSERT VAGUE ON DATE OF LAST FDA REVIEW

The FDA has chosen not to identify the date printed on the package insert as being either the date of the last reprint of the insert or the date of the last FDA review of the research data on the drug. The reader of a package insert, therefore, has no way of knowing if the package insert reflects the current state of knowledge regarding the drug.

• NO SYSTEM FOR RETRIEVING DRUG INFORMATION ACCORDING TO USE

The FDA has no ready means of identifying those drugs which the agency has approved for a specific use (such as for high blood pressure, diabetes, obstetrics, etc.), according to the Office of Consumer Safety. The FDA has chosen to store drug information in its computer according to the drug's generic (chemical) name and by the manufacturer's trade name, but not according to indication (approved use). In other words, the FDA has chosen not to store in the computer that information which could identify whether a drug has or has not been approved by the FDA for a specific use.

• FDA DOES NOT DISTINGUISH BETWEEN EXHAUSTIVE SCIENTIFIC INVESTIGATION AND CURSORY EVALUATION IN THE PACKAGE INSERT

The FDA has provided no system to enable the reader of the package insert to distinguish between those uses of the drug which have been subjected to a controlled scientific investigation, evaluation, and FDA review before being approved as safe by the FDA and those uses of the drug approved as safe by the FDA after relatively superficial testing and review, or because the drug is similar to a drug already on the market.

CAN THE CONSUMER GET THE PACKAGE INSERT?

• FDA QUIET REGARDING CONSUMER ACCESS TO DRUG INFORMATION

There is no state or federal law which prohibits the pharmacist from giving the consumer the package insert which comes in the carton of prescription drugs. However, the FDA has made no significant effort to inform the public that this information can legally be made available to consumers by pharmacists, or that the same information in the package insert can be found in the PHYSICANS' DESK REFERENCE, found in most libraries.

The enactment of state laws requiring the licensed pharmacist to offer the consumer the opportunity to read or copy the package insert of the prescribed drug, prior to purchase, would help the consumer to make a more informed decision as to whether to take or forego the drug.

• PHARMACISTS ARE REQUIRED TO SUPPLY FDA-APPROVED PATIENT PACKAGE INSERTS (PPIs) WITH ALL ESTROGEN DRUGS

To date, the FDA has not taken punitive action against pharmacists who fail to comply with the law. In the event of drug-induced injury, the pharmacist's failure to protect the consumer from harm may affect a court's decision if a lawsuit should be brought.

HOW SAFE ARE THE DRUGS ADMINISTERED TO CHILDBEARING WOMEN?

• MAJORITY OF DRUGS GIVEN TO PREGNANT WOMEN NEVER APPROVED BY THE FDA AS SAFE FOR SUCH USE

Although dozens of different drugs are prescribed for or administered to women during pregnancy, labor, birth, and lactation, approximately 12 have actually been approved by the FDA as "safe" for such use. As mentioned on page 1, the fact that the package insert mentions use of the drug during pregnancy, labor, birth, and lactation does not mean that the FDA has approved the drug as safe for such use. Unless the specific use in pregnancy, labor, birth, etc. is mentioned in the "Indications" section of the drug's package insert the FDA has NOT approved the drug for that purpose.

• NO DRUG HAS BEEN PROVEN SAFE FOR THE UNBORN CHILD

The Committee on Drugs of the American Academy of Pediatrics has cautioned that there is no drug, whether an over-the-counter remedy or a prescription drug which, when taken by or administered to a childbearing woman, has been proven to be without risk for the unborn infant.

• NO FDA REQUIREMENT THAT OBSTETRIC DRUGS BE PROVEN SAFE FOR THE UNBORN CHILD

The criteria used by the FDA to determine the relative safety or risk of an obstetric-related drug (a drug administered to women during labor and delivery) have not included a requirement that the drug be proven safe for the unborn child exposed to the drug in utero (in the womb). None of the methods currently accepted by the FDA to evaluate the effects of drugs on the offspring is sensitive enough to detect subtle neurologic damage, i.e., learning disability, minimal brain dysfunction, dyslexia, hyperkinesis, perceptual handicap, attentional deficit disorders, etc.

• FDA'S ILLOGICAL CODE OF ETHICS

The FDA has taken the position that it is unethical to test drugs in pregnant women by means of controlled clinical trials and follow-up. Yet the FDA approves the use of drugs as safe for use during pregnancy, labor, and birth without requiring an initial or subsequent long-term, controlled follow-up on a limited number of the exposed offspring to determine if there are delayed adverse effects of the drug.

● NEITHER "OLD" NOR NEW OBSTETRIC DRUGS (AND DEVICES) ADEQUATELY TESTED FOR SAFETY

Of those few drugs approved by the FDA as safe for use in pregnancy and obstetrics, there is no evidence that the FDA made its decision on the basis of appropriate, properly controlled, scientific investigation in humans. The safety of many "old" drugs used in obstetrics today was determined by studying the effects of the drug on men, postmenopausal women, and one or sometimes two species of animals and extrapolating those effects.

As previously mentioned, the FDA does not require, prior to giving approval of a drug for obstetric use, that a controlled investigation and long-term follow-up be carried out on infants exposed to the drug in utero (hereafter referred to as "the exposed offspring"). Such a follow-up is essential in order to determine whether a drug may have latent, delayed, long-term, adverse effects on the subsequent physical, neurological, and mental development of the exposed offspring. The FDA does not even require that such an investigation and follow-up be carried out to determine the long-term effects of the drug on the offspring of primates (whose neurologic system is closest to that of human offspring) before the FDA approves the drug as safe for use as an obstetric drug.

● FDA REHASHES OUTDATED, UNCONTROLLED DATA

Although there was no control group of healthy, unmedicated mothers included in the Collaborative Perinatal Project (1959-1965) to serve as a baseline against which to measure deviation from normal human development in the offspring, the U. S. Department of Health and Human Services and the FDA continue to examine that data rather than utilizing more current scientific methodology.

● FDA HAS NO WAY OF ACCURATELY DETERMINING THE BENEFIT/RISK RATIO OF AN OBSTETRIC DRUG FOR THE OFFSPRING

The FDA has not required the manufacturers of obstetric drugs to investigate the effects of their drugs on the subsequent physical and neurologic development of the exposed offspring beyond the first minutes of life. Therefore, it is impossible for the FDA to accurately determine the risk/benefit ratio of a drug as it pertains to the exposed offspring. Nor can the FDA know whether a drug's effect observed in the newborn infant is significant unless such an investigation and follow-up is carried out.

A minimum of 10 years would be required for such a follow-up. A drug's more subtle effects on brain function may not become apparent until the child reaches at least the age of eight, when the brain is called upon to carry out more analytic tasks, such as those necessary for mathematical division, etc. (Our experience with DES has taught us that it may take 20 years before we know the effect of a drug (or medical procedure) on the physical development of the offspring).

● OUTMODED METHOD FOR ASSESSING NEWBORN STILL ACCEPTED BY FDA

None of the current methods accepted by the FDA as evidence of safety have been proven effective in determing a drug's more dysmorphogenic properties – the ability of a drug to cause functional or structural abnormality. The FDA has traditionally considered the offspring to be essentially unaffected by drugs administered to the mother if the infant scores 7 or above (on a scale of 10) on the Apgar Scale at one minute after birth. The Apgar Scale rates two points each for normal: (a) heart rate, (b) respiration, (c) muscle tone, (d) response and (e) skin color. The rating is crude and subject to bias since frequently it is based on the opinion of those responsible for the infant's delivery.

The American Academy of Pediatrics' Committee on Drugs has cautioned that the Apgar Score will identify only the most gross signs of neurologic dysfunction or brain damage. A follow-up by the National Institutes of Health of over 50,000 children revealed that among the children subsequently found to have cerebral palsy, 43% had been diagnosed as normal when they were discharged from the hospitals' newborn nurseries.

● FDA IGNORES ITS OWN GUIDELINES FOR EVALUATING NEUROTOXICITY IN NEWBORNS

The FDA's own guidelines for the evaluation of drugs used in pregnant women and in children* note that drugs circulating in the bloodstream of the newborn infant can penetrate the infant's brain. Drugs trapped in the infant's brain at birth can adversely affect the rapidly developing nerve circuitry of the brain and central nervous system by altering the following brain processes:

(a) Neuronal maturation: the rate at which the nerve cells in the brain mature
(b) Cell differentiation: the process by which the brain cells develop individual characteristics and capacity to carry out specific functions
(c) Cell migration: the process by which the brain cells are guided into their proper place within the brain and central nervous system
(d) Dendritic arborization: the interconnecting of the branch-like nerve fibers as the circuitry of the brain is formed
(e) Myelinization of nerve fibers: the forming of an insulating sheath of myelin (fat-like substance) around the nerve fibers. This insulation helps to assure that the nerve impulses – the messages to and from the brain – will travel their normal route.

Any alteration in the development of the intricately complex nerve circuitry of the brain has the potential for permanently altering the way the brain processes and responds to information. Yet the FDA does not require the manufacturer to state in the package insert the fact that the delayed, long-term effects of the drug on the subsequent neurologic development of the exposed offspring are unknown.

---

* *"General Considerations for the Clinical Evaluation of Drugs in Infants and Children", HEW (FDA) No. 77-1977, U. S. Govt. Printing Off., Wash., DC 20402*

The implication of these changes in brain circuitry were succinctly stated by Dr. Donald Tower when, as Director of the National Institute of Neurological and Communicative Disorders and Stroke, he cautioned:

> "It is the biochemical circuitry – the biochemical messengers and the relevant nerve cells in the brain – that form the basis for mankind's behavior".

- "CRITERIA FOR EXCLUSION" PERMITTED TO BIAS RESEARCH CONCLUSIONS

The FDA appears to make no effort to evaluate how the "criteria for exclusion" (reasons for excluding an infant from the group to be tested) skew the findings of safety in regard to the infant. For example, many studies of FDA-approved obstetric drugs excluded from testing any infant born to a healthy mother who received an epidural block during labor if that infant showed evidence of severe intra-uterine trauma and/or an abnormal physical or neurologic condition at birth or during the postpartum period (the first days of life). These exclusions ignore the fact that the trauma and abnormal conditions observed in the infant could have been caused by the drugs administered to the mother during labor and birth.

WHO DETERMINES THE "SAFETY" OF OBSTETRIC DRUGS IN REGARD TO THE UNBORN INFANT?

- OBSTETRICIANS, NOT PEDIATRICIANS, DECIDE THE SAFETY OF DRUGS ADMINISTERED TO CHILDBEARING WOMEN

It is well recognized that it is the fetus and newborn infant who are most vulnerable to the adverse effects of obstetric-related drugs. Yet the FDA relies primarily upon its Fertility and Maternal Health Drugs Advisory Committee (FMHD), comprised essentially of obstetricians, for advice on the safety of new drugs and also of drugs currently marketed for use in childbearing women. No expert specifically concerned with the effects of obstetric drugs on the subsequent development of the exposed offspring nor any interdisciplinary consultants regularly attend the FMHD Advisory Committee meetings.

The obstetricians who make up the FDA's FMHD Advisory Committee are aware that if they recommend that the FDA remove its approval of a drug used in obstetrics, they will increase the possibility of malpractice litigation for themselves and their colleagues who have had "trouble" with the drug. Their own self-interest works against their recommending that the FDA remove its approval of a drug for use in obstetrics unless there is blatant evidence of danger.

- FDA REFUSES TO ESTABLISH A PERINATAL DRUG COMMITTEE

The FDA has no advisory committee or department which has the expertise to evaluate the effect on the child of drugs used in pregnancy and/or obstetrics. The FDA has refused repeated appeals to establish a multidisciplinary perinatal drug advisory committee to consider the effects on the child of drugs administered to the mother during pregnancy, parturition, and lactation.

HOW RELIABLE ARE THE PACKAGE INSERTS FOR OBSTETRIC DRUGS?

- FDA PERMITS MANUFACTURERS TO IMPLY THAT THE MAJOR RISK TO THE FETUS IS LIMITED TO THE FIRST THREE MONTHS OF PREGNANCY

The FDA permits manufacturers to use statements such as, "This drug should not be taken during the first three months of pregnancy", or words to that effect, which imply that the fetus is at risk for serious adverse drug effects only if the mother is given the drug during the first trimester of pregnancy.

While the formation of the fetal heart and other internal organs is relatively complete by the end of the first three months, the fetal brain and the nerve circuitry which make up the fetal central nervous system (CNS) are developing very rapidly around the time of birth. Therefore, the brain and CNS of the fetus and newborn infant are vulnerable to drug-induced damage at that time.

- EVASIVE WORDING PERMITTED IN PACKAGE INSERT

Manufacturers are permitted to use wording in the package insert which implies that a serious adverse reaction to the drug will occur in the mother, the fetus, or the newborn infant only if the mother is "hypersensitive" to the drug. In one recent study, one out of every four infants whose mothers received only 50 mg. of meperidine during labor (considered by many to be a minimal dose) showed signs of neurologic depression at birth.

The FDA permits manufacturers to state in the package insert that a drug has "no significant effect on fetal development" (or words to that effect) even though the manufacturer has made no effort to carry out, and the FDA has not required, a controlled scientific investigation and long-term follow-up of the exposed offspring to determine whether an observed effect in the newborn is or is not significant to the child's physical and neurologic development.

Another example of evasive wording permitted manufacturers by the FDA is the statement, "Safe use in pregnant women other than in labor has not been established" (or words to that effect). Such a misleading statement implies that the drug has been proven safe for use during labor when, in fact, no such proof exists.

- MANUFACTURERS PERMITTED TO BURY WARNINGS ON SERIOUS RISKS

The FDA permits the manufactuer of a drug frequently used in epidural block, etc. to note some of the drug's most serious adverse effects under the section of the package insert entitled "Allergic Reactions" far removed from the section entitled "Usage in Pregnancy" or "Use in Obstetrics", under which such adverse effects should be noted.

Under the section "Usage in Pregnancy", the text reads:

> "Safe use in pregnant women other than in labor has not been established".

One has to look much farther on in the package insert, under the section "Allergic Reactions", to learn of some of the risks involved when the drug is used for epidural and caudal anesthesia. Under "Allergic Reactions" the text reads:

> "Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery".

FDA officers responsible for approving and overseeing the drug and its package insert permitted the manufacturer to note these serious adverse effects under the section headed "Allergic Reactions". They continue to permit such inappropriate placement of this important information – long after the situation has been brought to their attention.

Despite the growing concern that regional block anesthesia (epidural, spinal, etc.) may be contributing to the rising rate of cesarean section in the U. S., the FDA has made no effort to investigate whether regional block anesthesia increases the need for cesarean section performed because of dysfunctional labor and/or fetal distress.

- MOST DANGEROUS EFFECTS OF OBSTETRIC DRUGS FREQUENTLY OMITTED FROM PACKAGE INSERT

The loss of the gag reflex is one of the most dangerous effects of obstetric drugs. If the drugged mother retches vomitus or gastric fluid and her gag reflex fails to prevent the acidic, caustic substance from being inhaled into her lungs, pneumonia or a life-threatening condition called "aspiration of vomitus" can result. This condition can also occur in the newborn infant whose neurologic system is depressed by its mother's obstetric drugs. Yet these effects are not mentioned in the package insert of those drugs which can cause these hazardous neurologic dysfunctions. (Administering an antacid to the mother during labor will reduce the acidity of her stomach but can create problems in itself.) The true incidence of suffocation or chemical pneumonia resulting from aspiration of vomitus is unknown. Death certificates are not always specific, and physicians are reluctant to report such occurrences to the FDA.

Another very dangerous but unmentioned adverse effect occurs when the obstetric drug is inadvertently injected into the mother's bloodstream, into the wrong area of her spine, or into the fetus itself. The result can be a neurologic shutdown for the mother or her baby. Yet the manufacturer is not required to note this very real possibility and its potential effects in the package insert.

These dangers are intensified if the anesthetic agent or block is administered by a nurse-anesthetist when no physician is present to handle a sudden, drug-induced emergency.

- TIME OF FETAL EXPOSURE TO OBSTETRIC DRUG NOT REQUIRED IN PACKAGE INSERT

With rare exception, those drugs administered to the mother during labor and delivery rapidly filter through the placental membranes and enter the fetal circulation and brain. The drugs and their metabolites, which for some drugs are equally hazardous, continue to circulate in the fetal blood, brain, and other organs during labor and for several hours or days after birth.

Yet drug manufacturers are not required to note in the package insert the average lapse of time between administration of the drug to the mother and the time the drug enters the fetal circulation. Nor are they required to note the number of hours or days the drug and its metabolites can still be detected in the blood of the newborn infant. This information is important to pediatricians and others caring for and prescribing for the newborn infant.

- BIOCHEMICAL FACTORS DETERMINE DRUG'S EFFECT

The effects on the unborn child of a drug administered to or taken by the pregnant or parturient (laboring) woman depends on many factors: (a) the skill and training of the health care provider, (b) the type and quantity of the drug, (c) when and how often the drug is administered, (d) the condition of the mother, the placenta, and the fetus when the drug is administered, (e) the interaction of the drug with other drugs, etc. If all biochemical factors are favorable, the development of the exposed offspring may not be affected, or at least not to any discernible degree. Unfortunately, it is impossible to predetermine how an individual fetus will be affected by a drug or combination of drugs administered to the pregnant woman.

CAN ONE GET A LIST OF THOSE DRUGS WHICH HAVE BEEN APPROVED BY THE FDA AS SAFE FOR OBSTETRIC USE?

- FDA UNABLE TO SINGLE OUT THOSE DRUGS THE AGENCY HAS APPROVED FOR USE IN OBSTETRICS

Until recently the FDA did not appear to show particular concern regarding the adverse effects on the fetus of the various drugs ingested by or administered to pregnant and parturient women. Efforts to obtain from the FDA a list of obstetric-related drugs which have been approved as safe for such use by the FDA have proven fruitless.

WHAT ABOUT THE FDA'S NEW RISK CATEGORIES FOR OBSTETRIC DRUGS?

- NEW CATEGORIES OF OBSTETRIC–DRUG RISK TEND TO GIVE FALSE SENSE OF SAFETY

The FDA has established five categories to indicate a drug's potential for causing birth defects. However, even drugs in Category "A" (the category of least risk, in which well controlled studies in women have failed to demonstrate immediate risk to the fetus) have not been tested to determine whether or not there are delayed, long-term risks to the physical and neurologic development of the exposed offspring.

WHAT ABOUT ULTRASOUND AND MEDICAL DEVICES SUCH AS FETAL MONITORS?

- SAME FLAWS SEEN IN FDA REGULATION OF MEDICAL DEVICES

The FDA has approved the use of ultrasound (high-frequency sound) for fetal imagery (sonogram) and monitoring during labor without requiring manufacturers of the devices to advise the physician and the patient that the delayed, long-term effects of ultrasound on the subsequent development of the fetus, and especially on the ova of the female fetus, are unknown.

The FDA cautioned against the unnecessary use of ultrasound in obstetrics in the official "Federal Register" (Vol. 44, No. 31, pp. 9542–9545, Feb. 13, 1979). FDA officer Dr. Marion Finkel summarized the FDA's concerns:

> ". . . animal studies have been reported to reveal that diagnostic levels of ultrasound cause a delay in neuromuscular development, altered emotional behavior, EEG (brain wave) changes, anomalies, and decreased survival".

The FDA has cautioned that ultrasound should not be used routinely — but only when there is a valid medical indication and should be confined to the lowest exposure levels consistent with obtaining essential diagnostic information. Yet the FDA has chosen not to bring these observed effects to the public's attention via the FDA Consumer magazine or by news release.

DOES THE FDA'S MAGAZINE FOR CONSUMERS DEAL TRUTHFULLY WITH THE RISKS OF APPROVED DRUGS AND DEVICES?

- FDA MAGAZINE FOR CONSUMERS WITHHOLDS INFORMATION ON RISKS

The FDA Consumer magazine, prepared and published by the FDA, frequently withholds from the public information on the serious side effects, risks, and pertinent areas of uncertainty regarding the drugs and devices discussed in articles which appear in that publication.

The information in this pamphlet may be disturbing, but it is information you will need for making informed decisions regarding your health care.

WHAT YOU CAN DO:

1. For information regarding a specific drug, ask your physician or pharmacist for a copy of the package insert or consult the PHYCIANS' DESK REFERENCE (PDR) at your pharmacy or local library. The information in the PDR is the same as that in the package insert, which is written by the manufacturer and approved by the FDA.

2. Check with your pharmacist as to the interaction of the drug with food, beverages, or other drugs you are taking.

3. Check with your local library for consumer-oriented books which discuss drug actions and interactions (i.e., "The People's Pharmacy", "Pills, Politics and Profits", "Women and the Crisis in Sex Hormones", etc.).

4. Save prescription labels. Keep a record of all drugs taken — brand name, generic name, amount prescribed, and number of times taken. In the case of pregnancy, keep a record of all drugs taken during pregnancy (beginning with the date of the last menstrual period), labor, birth, and breastfeeding. Remember, the overwhelming majority of drugs have never been evaluated for use in obstetrics.

5. In the event of hospitalization, obtain and preserve a complete copy of your hospital medical records. If hospitalized for childbirth, also obtain and preserve a complete copy of your infant's hospital medical records, including nursing notes, lab reports, brand name of fetal monitor (long-term effects of ultrasound are unknown), any x-rays, fetal monitor strip charts, etc.

In 1980 the following states had laws or regulations providing the patient with access to his/her hospital medical records from the hospital's Medical Records Administrator:

Alaska
Colo.
Conn.
Fla.
Ill.
Ind.
La.
Maine
Mass.
Mich.
Minn.
Mo.
Nev.
N J.
Okla.
Penn.
S. Dak.
Virg.
Wisc.

6. For information unavailable elsewhere, or to report an adverse drug reaction or a suspected drug-related birth defect, write to

Assoc. Commissioner, Office of Consumer Affairs
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

BIBLIOGRAPHY:

Final Report: Joint Commission on Prescription Drug Use, January 1980, Department of Health, Education and Welfare (DHEW).

Final Report: Review Panel on New Drug Regulation, DHEW, May 1977.

General Accounting Office Report, Evaluating Benefits and Risks of Obstetric Practices, HRD-79-85A, September 1979.

"The Brain", Scientific American 241: 44-246, September 1979.

"Medical Records: Getting Yours", Health Research Group, Wash., DC, 1980.

"Pregnant Patient's Bill of Rights", American Foundation for Maternal and Child Health, New York.

Prepared by Doris Haire, Chair, Committee on Health Law and Regulation, National Women's Health Network
Copies of this publication are available at $1.00 each (includes postage and handling) from either of the following organizations:

National Women's Health Network
224 Seventh St., S.E., Washington, DC 20003

American Foundation for Maternal and Child Health
30 Beekman Place, New York, NY 10022

Ms. HAIRE. During the preparation of my report I learned that most of the drugs administered to women during labor and birth have never been approved by the FDA as safe for such use and that none of these drugs has been subjected to a properly controlled, scientific evaluation and found to be safe in regard to the drug's effects on the offspring's neurologic development. The FDA does not require the manufacturer to demonstrate such safety.

At no other time in an individual's life is his or her brain more vulnerable to trauma and permanent injury than during the hours which surround that individual's birth. Other major organ systems are essentially formed by the first 4 or 5 months of pregnancy. It is the nerve circuitry of the brain and central nervous system of the fetus which is rapidly developing as labor begins, making these awesomely complex structures vulnerable to permanent damage from the drugs and procedures administered to the mother during that time.

Drugs administered to the mother during labor and birth rapidly filter through the placental membrance and enter the blood and brain of the fetus in a matter of seconds or minutes. While the fetus is connected to the mother's circulatory system, her system helps to eliminate the drug from their two systems. However, if a drug is frequently or continuously administered to the mother during labor, which it often is, there is a tendency for the drug to accumulate in the maternal and fetal blood and brain due to overload.

Once the infant is born and the cord is clamped, those drugs which are present in the newborn infant's blood and brain are essentialy trapped in the infant's circulatory system. Because the newborn's metabolic and endocrine systems are immature the infant cannot readily break down and excrete the drugs. The trapped drugs, or their potent metabolites, may continue to circulate in the newborn infant for several days or longer. One study by Rosenblatt shows the effect through a 6-week testing period so these are not short term effects. What does this prolonged exposure to maternally administered drugs mean to the later neurologic development and behavior of the offspring? Drug-induced biochemical alterations within the brain of the about-to-be-born or newly born infant have the potential for permanently disrupting the normal link-up of the baby's brain cells by altering the biochemical markers which guide the cells into their proper places. It is somewhat analagous to the unintentional spilling of a chemical over telephone wires which are being connected according to the color code at the end of each wire. The chemical removes the color from the wire ends. The technician must continue to connect the wires, not knowing exactly which wires to connect with which. The circuitry is completed; it functions, but imperfectly.

While the process of cell migration is not yet fully understood, present knowledge of neurobiology suggests that the normal biochemical message left along the pathway of the neuron by the preceding cell—as it travels to its proper place within the central nervous system—leave a biochemical message along the pathway which directs the next brain cell into place. Drug-induced changes in the biochemical message can disrupt this vital process.

Lesions, resulting from the death of cells due to drug-induced, prolonged reduction or deprivation of oxygen, can also disrupt the brain's circuitry by requiring the cells to find other routes by which to form the circuitry. I recently gave a talk to the Royal Society of Medicine in London and I found, in talking with the various physicians, that they assume that the major form of damage to the fetal brain is through hypoxia. I hope that one of the things that comes out of this hearing will be that more people will begin to appreciate the potential for obstetric drugs to disrupt brain circuitry in the exposed offspring.

There is no doubt in my mind that a significant proportion of the 4 million children and youths in the United States who are afflicted with significant mental and neurologic dysfunction are the victims of obstetric medications administered with the very best of intentions to the mother during labor and birth. Of the 4 million almost 1½ million are considered to be of normal IQ. So we are not talking about the retarded. We are talking about perfectly intelligent children who cannot learn by the ordinary methods.

The FDA's own guidelines for the evaluation of drugs used in pregnant women and in children, which I submit for the record, acknowledges that drugs circulating in the bloodstream of the newborn infant penetrate the infant's brain and that once in the brain the drugs can adversely affect the rapidly developing nerve circuitry of the brain and central nervous system by altering the following brain processes: (a) neuron maturation: the rate at which the nerve cells in the brain mature; (b) cell differentiation: the process by which the brain cells develop individual characteristics and capacity to carry out specific functions; (c) cell migration: the process by which the brain cells are guided into their proper place within the brain and central nervous system, and (d) dendritic arborization: the interconnection of the branch-like nerve fibers as the circuitry of the brain is formed.

[The material referred to follows:]

GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS IN INFANTS AND CHILDREN

I. GENERAL PRINCIPLES

A. INTRODUCTION AND OVERVIEW

The booklet entitled "General Considerations for the Clinical Evaluation of Drugs" contains much information which is applicable to drug testing in children and it should be considered a companion piece to this booklet.

To facilitate approval of new drugs for use in children testing should be related to the anticipated duration of usage and to the size and age of the pediatric population likely to be exposed to the new drug. Emphasis should be placed on elucidation of unexpected toxicity, not simply collecting examples of the types of toxicity predictable from knowledge of the pharmacologic properties of the drug. New and innovative forms of in vitro and in vivo testing should be employed because new agents developed today, which may exhibit some of the same forms of toxicity responsible for therapeutic catastrophies of the past, may not be identified as such by current testing procedures.

The design of studies must be flexible to recognize the need for evaluation of a new drug or substance for the treatment of rare diseases or diseases which are unique to the pediatric age group. In these circumstances, special considerations may include an abridgement of the usual requirements for safety and efficacy. Such abridgement should be considered when the use of the drug is limited to a few patients, particularly patients suffering from a disease for which no alternate therapy is available. In addition, an investigator concerned with such patients should be allowed considerable latitude to administer various substances, particularly naturally occuring amino acids, cofactors, and vitamins without extensive preclinical studies. Furthermore, if no appropriate animal model for a disease condition exists, and if efficacy is readily demonstrable (e.g. certain seizure patients), early efficacy studies in children are appropriate.

B. FACTORS AFFECTING BOTH SAFETY AND EFFICACY

1. Methods

Adequate methods for determination of the drug and its major metabolites (especially those which are pharmacologically active) in biologic fluids (especially serum and optimally in tissues) should be developed during preclinical or early clinical (phase I and II) testing. The particular method obviously will depend on the chemical nature of the drug, expected concentrations in serum, etc., but it should not require administration of radiation emitting substances. Assays based on techniques such as radioimmunoassay, gas-liquid chromatography, and competitive protein binding are at present the most likely to achieve the desired degree of accuracy, sensitivity, and reproducibility. Use of stable isotopes is a method of great promise, although the initial cost of equipment may be prohibitive except in research centers and the National Center for Toxicologic Research. The administration of radioisotopes to children is not to be generally condemned, but it should be avoided except under special circumstancs. Such techniques are of great value and entirely appropriate for special studies under appropriate circumstances. For example, use of tracer amounts of labeled (^{14}C, ^{3}H) amino acids, glucose, or other intermediary metabolites may be invaluable for defining metabolic diseases, and similar employment of labeled drugs could conceivably be employed. Use of isotopes, other than ^{14}C and ^{3}H, which have short half-lives and low-energy emission equivalent to a conventional chest- x-ray offer considerable promise and should be employed whenever possible.

The small sample volume obtainable, particularly from small infants, is a critical factor in the development of appropriate methods, particularly when multiple samples are required. This is not a prohibitive requirement and should not be used as an excuse to avoid development of appropriate assay procedures. Radioimmunoassays for drugs such as digoxin or diphenylhydantoin have been developed which utilize as little as 20 to 100 microliters of serum. The development of appropriate methods for determination of serum levels is particularly important for those drugs in which serum levels can readily be related to pharmacologic or therapeutic effects. In these instances, determination of serum levels is the key to studies of dose, dose interval, bioavailability (when coupled with urinary excretion), apparent volume of distribution, etc.

Methods should be continually reviewed, revised, and updated with the goal of developing methods appropriate for routine use in laboratories cooperating with the investigator, and such assays should become sufficiently standardized and simplified so they are within the practical capability of the clinical laboratory of any large hospital. Moreover, modifications should be directed toward identification and quantification of the principle metabolites of the drug, so comparison may be made with the elimination pattern of adults. If major differences exist, such studies would serve as a warning of possible adverse effects and should lead to attempts to identify the unique pathway of metabolism in the immature patient.

With certain categories of drugs - the so-called "hit and run" agents, such as the cytotoxic drugs, certain enzyme inhibitors, storage granule depletors, etc. - assays of serum levels are of little or no value. Therefore, requirements for assay methodology may be relaxed or waived. Other appropriate assays of biologic effect should be developed for these agents. For example, inhibition of incorporation of tritiated thymidine into white blood cells might be used as a measure of the effect of certain cytotoxic agents. Antibiotics and certain other chemotherapeutic agents have special requirements and methods for estimation of effective serum levels. Bioassay techniques are entirely appropriate as long as the method is scaled down to the small sample volume of pediatric patients. Techniques employing the patient's own pathogen as the test organism should be available for the use of clinical laboratories engaged in phase II and III trials.

2. Studies of Absorption, Distribution, Metabolism and Excretion (ADME)

Studies with varying degrees of depth and completeness, appropriate to the drug and its intended use, are essential for each age group and are described in detail in the respective sections. In general, the preclinical and early clinical phases should lead to accumulation of data which account in a major way for the disposition of the drug. Not every metabolite may be identified, and the intimate details of each of the ADME phases will not be elucidated. Judgment must be exercised about requirements for data which are clinically relevant, and not all drugs should be subjected to full investigation. However, the following data should be available for drugs which will be administered orally in divided doses for courses of one week or longer:

a. Absorption: From the physical nature of the drug and its pKa the influence of changes in pH of the stomach and intestine on the ionization and thus the absorption of the drug can be predicted and verified. When appropriate, the approximate percentage of a single oral dose absorbed should be determined. If easily studied and when of possible clinical importance, the area of the gastrointestinal tract where the drug is absorbed (i.e., stomach, terminal ileum, etc.) may provide useful information in predicting drug interactions and alterations in absorption in disease states.

b. Distribution: Binding to plasma proteins (affinity and percent bound at therapeutic blood levels), whether albumin, globulins, or special carrier proteins, and the percent of total serum concentration which is "free" should be determined. Distribution and particular propensity for accumulation or fixation to certain tissues (for example, tetracycline in bone and teeth) in developing and mature animals should alert reviewers of possible forms of toxicity so appropriate additional studies can be requested. Apparent volume of distribution may be useful in designing dosage regimens. Studies of dialyzability may be useful in developing recommendations for the management of overdoses and accidental ingestions.

c. Metabolism: The pattern of metabolites and the biotransformation reactions involved - that is, hydroxylation, demethylation, glucuronidation, etc. - should be known from studies in man. Requirements for toxicity studies in immature animals (especially rodents) should be limited, if possible, to a species for which experimental evidence has established a similarity by immature humans to the handling of the agent being tested.

3. Bioavailability

An important influence on studies of safety and efficacy is the bioavilability of different formulations and of different manufacturers' products. When the dosage form constitutes a new chemical entity, appropriate studies must be conducted in adults before children are exposed. The exact and total constituents of the final dosage form should be known. Studies of bioavailability should include, but not be limited to, determination of serum levels and the time of peak levels after a single dose. Total absorption is usually best determined by quantitative determination of the urinary excretion of the drug and its principal metabolites. Because of differences in pH, gastric emptying time, intestinal motility, etc., differences in bioavailability, especially between newborn infants and adults, should be duly considered and investigated when appropriate. Moreover, when changes in gastric or intestinal pH, flora, or motility might be reasonably anticipated to differ from normal because of disease or other factors, additional studies are indicated. Studies of bioavailability often may be sufficiently covered in conjunction with studies of absorption, efficacy, etc., and need not demand independent investigations.

The possible toxicity or influence on the pharmacologic properties of the drug by the vehicle and/or other components of the formulation (stabilizers, excipients, etc.) must be considered. This results from the fact that many drugs tested in the form of tablets or capsules in adults will be administered as suspensions, solutions, or elixirs to infants and children. Moreover, the vehicle or solubilizing chemicals in parenteral preparations must be considered as a possible source of uniquely toxic agents, particularly for newborn infants.

4. Drug Interactions

Interactions between drugs occur in a variety of ways, ranging from physiochemical incompatibilities to opposing or synergistic pharmacologic effects. Preclinical and in vitro testing can be expected to detect most interactions, particularly when coupled with phase I and II testing in adults. However, especially in neonates, age-dependent differences in pharmacokinetics may result in unique interactions. For appropriate review of a new agent, the types of drugs which may be used in conjunction with the proposed agent for the same disease or condition at different ages should be considered to completely evaluate possible drug interactions.

Physicochemical interactions will probably be detected in early work with the new drug. Of particular concern in pediatric usage would be interactions which might interfere with the absorption or action of vitamins, trace minerals, essential amino and fatty acids, or other constituents of infant formulas and other dietary sources.

Physiologic or pharmacologic actions which might further impair the normally limited capacity of the neonate to metabolize and/or excrete drugs would be of particular concern. Specifically, inhibition of or competition for hepatic biotransformation reactions occurring via the mixed-function oxidase system and/or the glucuronide conjugating system, or decreases in glomerular filtration rate or tubular secretion can be predicted to have important consequences for the newborn.

Further interactions of particular concern to newborn infants relate to bilirubin, particularly with drugs administered near term, at delivery, or directly to the newborn. Binding to albumin with displacement of bilirubin and enhanced neurotoxicity is known to occur with a number of anionic compounds. Other factors (e.g., hypoxemia and acidosis) have also been reported to increase the potential toxicity of bilirubin. Moreover, binding by drugs might interfere with the transport and action of endogenous substances other than bilirubin (cortisol, thyroxin, fatty acids, etc.) and with the binding of other drugs.

5. Enzyme Induction

The importance in pediatrics of the induction of hepatic drug-metabolizing enzyme activity by exposure to drugs and chemicals is unclear at present. Three hundred or more drugs and chemicals are known to produce [illegible] increases in liver size, proliferation of smooth endoplasmic reticulum and increases in the specific activity of mixed-function oxidase and glucuronyl transferase enzymes in experimental animals. In clinical studies, small changes in serum concentrations and half-life for a few drugs have been reported in adults, although some negative reports have appeared.

Almost nothing is known about "inducibility" at various ages in man. Decreases in serum bilirubin levels have been reported in congenital nonhemolytic jaundice and in normal infants with "physiologic" jaundice treated with phenobarbital, nikethamide, and DDT. Increased smooth endoplasmic reticulum in hepatocytes and increased NADPH cytochrome c reductase (a microsomal enzyme) activity have been shown in infants treated with phenobarbital. Similarly, increased glucuronidation of salicylamide has been reported. Thus, the infant can respond to exogenous "inducing" agents although the details of the process and the extent and the clinical importance of this reponse remain unclear.

When induction is considered relevant, noninvasive types of studies, such as antipyrine half-life as determined by salivary concentrations or urinary excretion of the hydroxylated metabolite, may be undertaken. The urinary excretion of 6-hydroxycortisol or D-glucaric acid may also be used as monitors. Invasive techniques - such as direct determination of serum half-life or, rarely, liver biopsy obtained adventitiously - may yield more direct data.

C. EFFICACY

Because of ethical considerations, reasonable evidence of efficacy generally should be known before infants and children are exposed to the agent. Testing against the best known agent will be the preferable method for establishing efficacy with many drugs. A drug may be useful for only a certain percentage of the population diagnosed as having a general broad category of disease. For example, it is entirely possible that only a relatively small percentage of the "disease" population with bronchial asthma (a disorder probably of multicausal etiology resulting in similar clinical manifestations) may benefit from a particular therapeutic agent. In contrast, evaluations of efficacy at times may deal with an extremely small population. For example, a useful agent might demonstrate efficacy after study in only a few patients with a rare aminoacidopathy. Therefore, the requirement for demonstration of efficacy must not deal with fixed numbers. Again, flexibility must underline decisions about the number of subjects in each phase.

Based on ethical considerations, sick children rather than well ones will be the principal source of the experimental population, therefore, placebo groups cannot always be employed. Obviously, therapy cannot be withheld or an inactive drug cannot be administered by injection or other painful procedure. A number of alternative methods to the classical double-blind placebo experimental design can be suggested. In many instances, a standard drug can be used for comparison. Historical group controls may be utilized. "No drug" crossover can be used if the patient can tolerate a "no drug" period without serious compromise of his health. At times, the patient may serve as his own control, either as a personal historic control or in a "crossover drug/no drug" or "drug/standard drug" design. The drug may be most importantly compared to other therapeutic modalities, for example, behavioral modification, psychotherapy, dietary manipulation, and so forth.

Specific types of diseases where efficacy is likely to be tested are described for each age group in Section II.

D. EXPERIMENTAL DESIGN

Ethical, practical, and legal considerations may preclude studies by the most theoretically ideal experimental approach. This fact need not be viewed as an insurmountable obstacle because drugs should optimally be tested under conditions of actual clinical use, whether administered to hospitalized patients or in office practice. Such considerations do not obviate the need to establish a rigid protocol, including appropriate controls of whatever type, evaluating dose response phenomnena, and adhering to sound experimental design.

Study design must: (1) account for adequate control of variables and include appropriate statistical procedures, (2) detail methods and provide validation for assessment of benefit, (3) allow for handling of adverse or side effects, and (4) demonstrate awareness of the placebo response, both for beneficial and for adverse effects.

Perhaps the single most important variable to be assessed and controlled is the comparability of the study populations. This must be assessed in terms of a variety of parameters appropriate to the study, at times including but not limited to disease, social, physical, intellectual, and behavioral equivalence.

The mechanism(s) for evaluating adverse effects, whether by means of volunteered or elicited reports, questionnaires, or other means must be clearly stated and appropriate for the age group(s) under study.

Provision should be made for the management of accidental or intentional overdosage and severe, acute toxic reactions. Dialysability, specific antidotes, and other therapeutic measures should be assessed, and such information should be included in the protocol which is available to all involved in the study.

There should be safeguards to ensure that any study can be terminated at the earliest possible moment if danger to the subjects arises.

Studies of blood, liver, and renal function should be selective and appropriate for known modes of action and toxicity, rather than the accumulation of a mass of laboratory data from samples obtained by venipuncture or other painful procedures which are then run through the autoanalyzer. Initially, a wide base of studies may be used; but, if these studies are negative, only a few highly selective parameters should be monitored. A similar approach is suggested for the use of ECG, EEG, and other time-consuming and expensive studies.

II. SPECIFIC AGE-DEPENDENT FACTORS INFLUENCING SAFETY AND EFFICACY

Growth from conception to adult life involves complex changes in anatomy, physiology, bichemistry, and behavior which vary considerably from one state of development to another. Therefore, the action and adverse actions of pharmacological agents will vary as absorption, distribution, metabolism and excretion, and receptor sensitivity are altered by the changes associated with growth and development.

In recognition of these developmental changes, this portion has been written in sections; periods of childhood have been divided into stages which share characteristics distinguishing each stage from the other stages. In each stage, factors which may influence the disposition and action of a drug and the major immediate, delayed, and adverse actions are related to the major biologic events of the stage.

By introducing these age groups, it is not suggested that each drug be tested in each age group; rather, this is an attempt to ensure that the important biologic characteristics of the age(s) in which the drug eventually will be used therapeutically will be considered in evaluating both its beneficial and its undesirable effects.

Each age group will be evaluated as follows:

1. A General Statement of the biochemical, physiologic, and behavioral characteristics of the age group; specific ways in which the child is unique at the stage will be given.
2. Safety Considerations of particular importance to the age group. These are divided into three subgroups relating to the type of toxicity encountered and the temporal relationship of these effects to the initiation of therapy.
    a. Immediate Toxicity: Signs and symptoms occur soon after the initiation of therapy.
    b. Delayed Toxicity: Toxic effects occur only after a period of chronic administration. Certain adverse effects which occur in the immediate period of administration but manifest themselves later (such as tetracycline staining of the teeth) are also included in this category.

c. Late Onset Toxicity: Toxicity which becomes apparent months to years later, e.g., adenocarcinoma of the vagina in girls born to mothers who received diethylstilbestrol during pregnancy.

3. Efficacy

Means of establishing the beneficial effects of a drug and particular forms of desirable therapeutic activities.

4. Problems in Drug Evaluation

Special problems which may arise in the evaluation of drug action in a given age group.

5. Ethical Considerations

Special ethical considerations pertinent to each age group are delineated.

A. INTRA-UTERINE (CONCEPTION TO BIRTH)

1. General

The administration of drugs to the pregnant woman presents a unique problem to the physician. He must consider maternal pharmacologic mechanisms, and he must be aware of the fetus as a recipient of the drug. In therapeutic endeavors directed toward maternal disease, consequences of drug usage have often been unexpected; and adverse effects have appeared in the developing fetus, for whom the drug was not intended. On the other hand, the possibility of development of drugs for the treatment of fetal disease diagnosed in utero should be considered, and guidelines should be developed for the evaluation of both efficacy and safety of this type of compound when it is administered either via the maternal route or directly to the fetus. Drugs may also be administered to women who are not aware they are pregnant.

2. Safety and Efficacy

Adverse effects of drugs on the fetus vary depending on the stage of intra-uterine development. Before implantation, drugs may appear in high concentrations in tubular fluid and lead to the death of the fertilized ovum. Drugs which cause an adverse effect during organogenesis may result in anatomic malformations. Drugs given beyond the period of organogensis may affect the fetus and cause a functional disorder which is not associated with any known anatomic malformation.

Suggested methods of procedure to evaluate drugs which may be given to the mother during intra-uterine development are given in the following paragraphs. A prerequisite to intra-uterine studies for any new drug is evaluation (phase I and II) in adult men and in nonpregnant women of childbearing age.

Organogenesis--To evaluate drugs which will be used in pregnant women during the period of organogenesis, pharmacokinetic studies should be conducted in animals, including a subhuman primate. Localization of the drug within the fetus may be readily accomplished using isotopic techniques. At the same time, although not mandatory, studies of drug metabolism and disposition within the human fetal-placental unit should be considered.

The next stage of intra-uterine development to be considered for drug evaluation is from the completion of organogenesis to the onset of labor. This separation from the other periods of intra-uterine life is arbitrary because there will be drugs used throughout pregnancy for the management of maternal or fetal diseases. In addition to preclinical ADME tests, studies are suggested to delineate pharmacokinetics within the maternal-fetal-placental unit.

Effects on uterine blood flow should be assessed because of the importance of this parameter for considerations of safety. A current method which permits this assessment uses chronically catheterized sheep. Studies of drugs designed for direct administration to the fetus should be conducted in animals with the development of distribution and dose-response interrelationships. For clinical studies, evaluation should be carried out in those instances in which maternal or fetal disease warrants use of the drug. The first patients who undergo this phase III type of study should have careful evaluation of fetal heart rate via continuous electronic monitoring. Other physiologic parameters of the fetus should be followed during the period of drug administration insofar as technology permits. These pregnancies should be carefully followed, and the outcome should be meticulously ascertained - irrespective of whether the drug is administered for the duration of pregnancy or not. The infant should be carefully followed after birth until psychologic and physiologic development can be satisfactorily assessed. The state of fetal well-being should be assessed throughout pregnancy after the drug has been administered, whether singly or on multiple occasions, by measurement of urinary estriol excretion. Intrauterine growth should be assessed via noninvasive techniques, such as ultrasound. Pregnancy should be monitored by whatever means are technically available, commencing with the initiation of drug administration. This will permit determination of the time at which adverse effects occur, should such events take place. Evaluation of drug disposition will be greatly aided during this stage of development if advantage can be taken of pregnancies terminated by abortion by purposefully administering the drug just prior to termination.

Evaluation of drugs to be used for the management of labor and delivery--At this stage of development, direct assessment of effects of the drug on fetal physiologic processes (heart rate, respiration, activity) are possible, as is determination of concentrations of the drug and possible biochemical alterations (pH, glucose, etc.) in the fetus via sampling of scalp blood. Infants should be intensively evaluated at birth and throughout the neonatal period, with particular attention paid to their adaptation to extra-uterine life. This includes examination of acid-base status, weight gain, feeding ability and general activity, assessment of behavior by direct observation and through the use of psychometric tests which are valid for the neonatal period, and electroencephalography (EEG). Pharmacokinetic studies regarding drug disposition, metabolism and elimination should also be undertaken in these infants because they will have received the drug transplacentally shortly before birth. Determination of biologic half-life, excretion of the drug and its metabolites (including identification of the major metabolites in urine), and assessment of pharmacodynamic effects of the drug, if present, may be important for certain agents. Since most agents used at this stage of development are analgesics or anesthetics, careful examination of the functioning of the central and automic nervous systems is indicated. By intensive and comprehensive investigation of a few infants, followed until assessment of drug effects on psychologic and physiologic development can be made with validity, a determination can be made about the advisability of continuing trials of the drug during labor and delivery.

In the pregnant human female, studies at this stage of development can be undertaken by several different approaches. Women who receive the drug for therapeutic purposes and happen to be pregnant should be noted. Despite attempts made to avoid this situation, it will occur. The utmost advantage should be taken of this situation. Infants exposed in utero in this manner should be carefully examined at birth and followed with extensive psychologic and physiologic evaluation. This will enable ascertainment of adverse effects other than those noted at delivery. Evaluation at delivery usually detects only gross anatomic malformations.

The second approach to drug evaluation during this period of intra-uterine life involves administration of the drug to the mother, usually as a single dose, when termination of pregnancy is planned. In this instance, drug distribution, localization within the fetus, and metabolism within the fetal-placental unit can be examined. Metabolic products should be defined within the fetal-placental unit to determine whether drug biotransformation differs from that occurring in the adult. The use of radioisotopes may be permissible because of the termination of pregnancy. In cases where there has been repeated administration of a drug to treat a maternal illness, and subsequent therapeutic or elective abortion occurs, careful histopathologic study of the aborted fetus may detect adverse effects on organogenesis.

A third approach involves careful assessment of infants receiving the drug in utero because potential therapeutic benefit for the mother was sufficient to warrant the unknown risk involved in drug administration to the fetus. Such infants should be examined meticulously at birth and followed carefully thereafter until such time as satisfactory evaluation of effects on psychologic and physiologic development can be made. The duration of this follow-up will depend on the availability and sensitivity of testing devices, the nature of the drug and its known pharmacologic, toxic and teratologic effects.

3. Special Problems

In the preceding paragraphs it has been implied that drugs will be administered mainly for therapeutic benefit of the mother. The same considerations which apply to the design and execution of clinical trials during phase II are applicable, including controls, randomization, etc. Pregnancy per se should not preclude women from participating in Phase III studies when potential therapeutic benefit of a new agent may be obtained. Special attention must also be given to the effects which pregnancy itself may exert on drug action during the randomization of phase III clinical trials.

Agents will be developed solely for the benefit of the fetus. Determination of efficacy and safety will be difficult, but objectivity demands careful assessment of such benefit in controlled trials following drug disposition studies in pregnant animals (including primates). The considerations of safety outlined for intra-uterine development are applicable when drugs are administered for the benefit of the fetus. Dosage may have to be altered considerably when the drug is administered directly to the fetus via either amniotomy or intraperitoneally. The diagnosis must be firmly established prior to administration of drugs for the treatment of fetal disease. In addition, potential benefit from the drug will have to be sufficient to warrant the risks of administration directly to the fetus.

B. NEONATAL (BIRTH TO ONE MONTH)

1. General

Newborn infants have been shown repeatedly to be much more sensitive than adults to various pharmacologic agents. This has been most often the result of differences in pharmacokinetic processes. A number of other basic considerations, including receptor sensitivity, may also account for this phenomenon. The few available data show some of the pharmacokinetic differences peculiar to neonates. They include differences in general metabolism, inequities caused by dissociation of gestational from maturational ages, a larger body surface to body weight ratio, variation of protein concentration and drug-protein binding affinity, the presence of fetal hemoglobin, immature renal tubular function, and changes in pharmacodynamic response. Small infants are most susceptible to changes of ambient temperature, and the subsequent decrease in body temperature may have notable effects on the rates of drug metabolism and excretion. Moreover, the major variations of fat and water content in the newborn and between individual neonates may result in differences in distribution and subsequent kinetics.

2. Safety

a. **General Considerations of Safety:** The alterations in absorption, distribution, metabolism, and excretion in the neonate may lead to accumulation of the drug with resultant toxicity. Modification of dosage may avoid this type of adverse effect. The unique physiologic state of the neonate (particularly during illness) and the wide ranges of such pharmacokinetic determinants as pH, blood gases, electrolytes, protein concentrations, and temperature present additional possibilities which may result in toxic manifestations. The very rapidity of change of such determinants makes it necessary to provide assay methods of minimal sample size.

b. Specific Toxicities

(i) Central Nervous System Effects: Evidence exists for the enhanced penetration into the brain of many drugs. The cardiovascular, respiratory, and thermo-regulatory mechanisms are extremely sensitive to depressive effects in the neonate. In addition, neuronal maturation, cell migration, dendritic arborization, and cell differentiation are occurring at this age and may be affected by drugs and/or their metabolites.

(ii) Cardiovascular

Cardiogenic effects - Drugs may affect cardiac contractility, rate, and rhythm, thereby causing severe or possibly fatal adverse drug reactions. This has been a particular problem with local anesthetic agents used during delivery. The neonate may also display delayed CNS depression or the induction of seizures and unexpected excitation resulting from the administration of some agents; he may also become addicted or dependent.

Circulatory adjustment occurring during the change from the intrauterine to the extra-uterine environment may be hampered by the presence of certain drugs. In particular, closure of the ductus arteriosus may be impaired if respiratory depression results in hypoxemia and acidosis.

(iii) Metabolic Derangements: Changes in serum glucose, calcium, pH, sodium, potassium, etc. may be the result of drug-induced alterations in the infant's metabolic processes or may influence drug evaluation. Metabolic data obtained during the care of the sick newborn infant may provide valuable information in assessing safety and efficacy.

(iv) Changes in Bilirubin Kinetics: Prior to administration of any drug to the neonate, it is mandatory to study the drug in its final dosage form and, if possible, its metabolites and protein bilirubin binding. When appropriate, effects of the drug on conjugation, uptake, excretion, and enterohepatic circulation of bilirubin should be performed.

(v) Dermatotoxicity and Persorption: The topical application of pharmacologic agents to the neonate must be approached with an awareness of two peculiarities of this age group. First, the skin is more susceptible to dermatotoxicity expressed as photosensitivity and various forms of rash, including bullous eruptions. Second, the thin or absent statum corneum allows increased persorption, leading to systemic concentrations which may exert a toxic effect on other organs (e.g., hexachlorophene and brain damage). In addition, systemic reactions (e.g., cyclopentolate with atropine-like toxicity) may result from increased drug absorption through mucous membranes.

(vi) Gastrointestinal: Evaluation of the effects of a drug should include consideration of such adverse effects as the inhibition of gastrointestinal motility, change of flora, vomiting, or a malabsorption-type syndrome caused by direct irritation, as well as effects on absorption of nutrients.

(vii) Hematologic: Methemoglobinemia, thrombocytopenia, and hemolysis (especially in G-6-PD-deficient neonates) may be induced in the neonate necessitating investigation of this potential in the evaluation of new agents.

c. Drugs in Breast Milk: Most, if not all, drugs administered to the mother are excreted in the breast milk. Concentrations of the drug and/or of its metabolites should be determined with due regard for the individual variations of lactation volume itself. The mere presence of the agent in the breast milk does not necessarily indicate any effect on the neonate, deleterious or otherwise, and should not in itself mitigate against approval for use in lactating women. Various factors such as concentration, the total dose delivered, the absorption by the infant, etc. must be considered in evaluating potential effects mediated through breast feeding.

d. Delayed Effects: Consideration of long-term postmarketing studies on cognitive, behavioral and physical growth depends upon the nature of the drug.

3. Efficacy

Survival rates from severe illnesses such as neonatal sepsis, idiopathic respiratory distress syndrome, erythroblastosis fetalis and hemolytic disease of the newborn, and necrotizing enterocolitis may be the only measures of efficacy available.

4. Special Problems

Some major obstacles to be overcome in establishing efficacy and safety in this age group are:

a. The Influence of Maternal Disease: The variations in physiologic states of the neonate, secondary to the pathophysiologic conditions of the mother (e.g., infants of diabetic mothers) may (1) negate the random assignment of infants to controlled, matched study populations, and (2) alter the pharmacologic response of the infant to an administered agent.

b. The Influence of Infant Disease: The wide variability within each disease state and the relatively small population of affected individuals in any single institution, together with the marked influences of the host subject in terms of gestational and maturational ages, etc., present limitations in study design, random assignment, statistical analysis, etc.

5. Ethics

The neonate presents a number of unique ethical problems. Among these are:

a. The possibility of unusual toxicity and the extreme difficulty in identification of such a problem. The late appearance, the inability of the subject to exhibit common early signs of toxicity, and the inability to verbalize symptomatic complaints all contribute to the dilemma.

b. The higher risk potential inherent in this population dictates the most substantial evidence of benefit to be derived from the use of a new drug.

C. INFANT/TODDLER (1 MONTHS TO 2 YEARS)

1. General

This period is characterized by notable increments in physical growth and rapid maturation of all organ systems with associated functional change. Noteworthy in these regards are the central nervous system and the immune system. Of direct relevance to the effect of a drug on infants in the early months of this age group are alterations in protein binding and drug metabolism.

2. Safety

a. Immediate Drug Toxicity

(i) Difficulty in detecting toxicity by clinical assessment: Toxicity may or may not be apparent in infants, especially in the early months of this age group. This may be particularly true for central nervous system toxicity. Therefore, blood levels of pharmacologic agents should be monitored and cautiously interpreted because therapeutic blood levels for older children and adults may not be safe for infants.

(ii) Gastrointestinal tract: Acute and chronic gastroenteritis is frequently encountered in this age group. Certain drugs are more likely to cause diarrhea in infants than in older children. Gastroenteritis will affect drug absorption and may complicate interpretation of efficacy and toxicity. Dehydration with resultant hypovolemia, a frequent consequence of gastroenteritis in infants, may affect drug distribution and serum concentrations.

(iii) Central nervous system: Drugs may affect myelinization and brain differentiation, which are actively occurring in children of this age group. Such effects may not be limited to drugs which localize in the central nervous system or which exhibit a predominant effect on the brain.

b. Delayed Reactions

(i) General: Toxicity is difficult to assess in this age group by clinical observations alone. Furthermore, it may not be possible to distinguish adverse effects following any single dose in a repeated series of drug administrations because of delayed reactions. Although this problem also applies to older age groups, it is particularly pertinent to infants because of their relatively immature organ systems and their limited ability to communicate.

(ii) Hypersensitivity: In this stage of initial exposure to foreign protein (e.g., foods and inhaled particulate protein), drugs may predispose to hypersensitivity through such diverse mechanisms as inhibition of secretory antibody production or induction of partial blockade of beta adrenergic receptors.

(iii) Physical growth: Physical growth may be affected by various classes of drugs such as adrenocorticosteroids and tetracycline antibiotics. Consideration of long-term postmarketing studies on cognitive, behavioral and physical growth depends upon the nature of the drug.

3. Efficacy

Although easier than for the neonatal age group, evaluation of efficacy is far more difficult than in adults. Infants cannot cooperate in a number of commonly used tests of pharmacologic action; therefore, indirect parameters (e.g., length of illness, length of hospital stay, frequency of complications and subsequent disability), and certain laboratory tests will, of necessity, be used to determine efficacy.

4. Special Problems

a. Deficiency States: The presence of iron-deficiency anemia and diminished concentrations of certain serum proteins is more likely to occur in this age group than in any other age group. Such deficiencies may alter drug kinetics.

b. Breast-feeding: The possibility of interaction from chemicals, hormones, and drugs in breast milk should be considered when suckling infants participate in drug evaluation.

5. Ethics

Before evaluating new drugs in infants, substantial evidence of benefit or superiority over accepted agents should be demonstrated in older children and adults because infants may have a higher risk potential. Included among these increased risks are those pertaining to physical growth and neurological and intellectual development.

6. Other - Research Needs

Certain research needs can be identified as relevant to the study of new drugs for this age group. (a) Relatively noninvasive techniques for determining blood levels (e.g., salivary drug concentration) should be sought; (b) noninvasive techniques for establishing efficacy of a drug should be developed; (c) much additional information is needed on the effect of drugs on the development of the immune response (both humoral and cellular components).

D. CHILDHOOD (2 YEARS TO ONSET OF ADOLESCENCE - 12 YEARS)

1. General

This age group is characterized by slower growth and the highest incidence of infectious diseases. Increasing motor and social independence results in exposure to environmental hazards which lead to various accidents such as poisoning, burns, drowning, and physical trauma. Cognitive processes involved in school performance and school attendance - vital to intellectual and psychosocial development - are being rapidly acquired. At the end of this age period, rapid bone growth and epiphyseal maturation occur secondary to changes in endocrine activity. Accordingly, pharmacokinetics may differ from the infant and adolescent age groups, depending on the characteristics of the drug and the child's age within the broad age range of this period.

2. Safety

a. General: Safety considerations in general differ little from those in Section I. A specific need at this age, when accidental poisoning is common, is information dealing with acute toxicity and treatment of drug poisoning.

b. Specific Toxicities

(i) Immediate drug toxicity: A disease for which a drug is given may enhance its toxic potential. Thus, interaction with disease states which would apply particularly to drugs used at this age should be studied, e.g., antibiotics, bronchodilators, antihistamines, and anticonvulsants. An example would be the altered toxicity of ampicillin when employed in infectious mononucleosis or increased toxicity of isoproterenol (ventricular tachycardia) when the patient has hypoxemia and acidosis.

Hypersensitivity manifested by anaphylactoid and anaphylactic reactions are more likely to occur at this age and in adolescents than in younger children because of longer periods for sensitization and greater exposure to antibiotics and similar substances to which antibodies may be induced.

(ii) **Delayed Reactions**

Hypersensitivity manifested by serum sickness or drug fever--This may be seen with a variety of agents ranging from antibiotics to anticonvulsants and is common in this age group and in adolescents.

Drugs interfering with school performance and other childhood activities--These may include, but are not limited to, side effects which interfere with attention span (e.g., drowsiness) or reduce perception (e.g., tinnitus and decreased hearing).

Drug-nutritional interactions--The prolonged use of a drug in a child may affect his nutritional requirements. Recent observations on the rachitic effect of long-term administration of diphenylhydantoin illustrate this concern.

(iii) **Late Onset Reactions**

Chronic administration of a variety of agents may affect linear growth and/or weight gain.

Selective growth changes include advancement or retardation of puberty or of menarche.

3. Efficacy

Evaluation of efficacy based on objective criteria is possible in the school-aged child who is able to cooperate. Objective measurements should be stressed in study design. School performance and school attendance provide additional parameters which may be extremely useful in determining efficacy. Even though the rate of physical growth has slowed in this age group, changes in growth rate may provide additional evidence of efficacy, especially in those diseases which depress linear growth or interfere with normal weight gain. Assessment of osseous development (e.g., bone age) is one parameter of growth that may be useful where indicated. The efficacy of agents in preventing or altering morbidity from infectious diseases may be best studied in this age group when the incidence of viral and bacterial infections is high.

4. Special Problems

Accidental poisoning and overdosage are of prime consideration at this age. The manifestations of acute poisoning with the drug and its metabolites can be studied in juvenile animals. Information concerning specific antidotes and therapy of overdosage (e.g., peritoneal dialysis) should be included in the protocol and ultimately in the package insert.

5. Ethics

Special ethical consideration in this age group involves school absenteeism for studies as well as the psychological effects of such studies on the child. These should be discussed with parents before informed consent is obtained. Older children may be able to participate in the consent process.

E. ADOLESCENT (ONSET OF ADOLESCENCE TO ADULT LIFE - 12 TO 18 YEARS)

1. General

Adolescence may be defined as the transition period in which the child undergoes changes in physical, sexual, and psychosocial development transforming her/him into an adult. During this time period, the child's body is rapidly changing in form, undergoing final rapid growth to mature stature and the development of secondary sexual characteristics. Coupled to the dramatic changes in body form, the adolescent develops a new perception of her (him)self as an individual in relation to her/his niche in the family and in the general fabric of society.

Changes in physiology may produce alteration in the absorption, distribution, metabolism, and excretion of drugs as well as in receptor respose. The development of puberty and the known effects of sex hormones on drug metabolism warrant consideration in drug evaluation in the adolescent.

2. Safety

a. General Considerations of Safety

The major concerns relating to drugs given to an adolescent involve:

(i) the potential for abuse;

(ii) the possibility that the agent may alter the final stages of physical and endocrine development completing the growth cycle to maturity.

In addition, in this age group, medication may not be taken as prescribed. The adolescent frequently omits doses of medication, takes it at erratic intervals, and may take more than prescribed. Safety considerations should be addressed not only to the therapeutic dosage, but also to the consequences of suboptimal dosage and overdosage.

b. Effect of the Age Group on Safety Considerations

(i) Immediate Adverse Effects

Drug misuse includes that of accidental or intentional overdosage or underdosage and that of inappropriate use. The adolescent may fail to take the medication as frequently as prescribed, or he may employ it in larger doses than prescribed or for inappropriate reasons. The effects of such practices on the disease process and adverse effects will have to be anticipated.

Hypersensitivity reactions include anaphylaxis, serum sickness, and contact dermatitis. Although not unique for the age group, these reactions may occur as a result of self-medication or inappropriate routes of administration of medication.

(ii) Delayed Reaction

Dependency and habituation are among the major delayed reactions.

(iii) Late Adverse Effects

Psychosocial and behavioral alterations may occur as a late, even unexpected, action of a drug and should be considered in drug evaluation. These may occur either as a direct effect or as an exaggeration of an underlying problem.

Other--Growth changes, advancement or delay of puberty and of menarche, and effect on fertility may consitute other delayed drug reactions in this age group. Consideration of long-term post-marketing studies of possible drug effects in these areas depends upon the nature of the drug.

Pregnancy test on female participants--Because of the presence of unknown or hidden early pregnancy, adolescent girls should have pregnancy tests before entering any drug trials.

3. Efficacy

The same objective measurements used in adult patients to define efficacy should be used.

4. Special Problems

a. General: The plasticity of evolving form and functions in the adolescent produces unique therapeutic problems for this age group which can be grouped into three major categories.

(i) Drugs used to alter physical growth and sexual development. Drugs given to regulate growth or secondary sexual manifestations are unique to the adolescent. Many pharmacologic agents are employed in an attempt to make the subject "normal" or "superior" regarding growth, muscular development, or sexual development. Pressures to use drugs are generated by the adolescent's peer group. An adolescent who is too tall or too short, too obese or too thin, or not athletic enough is made the object of derision by his or her peers. Synthetic androgens are often used under these circumstances. Their effects on hepatic function (and metabolism of other drugs) and hepatic carcinogenesis should be taken into consideration.

The problems of potentially tall girls and of irregular menses may both be treated with synthetic sex hormones. The long-term effects of these practices must be studied with regard to fertility and carcinogenesis. The latter is highlighted by the development of uterine carcinoma in patients with Turner's syndrome after stilbestrol treatment.

Conditions affecting both males and females are obesity and sexual precocity. Growth and fertility could be affected by agents used in their treatment. For example, medroxyprogesterone - used in treatment of sexual precocity - has been shown to suppress the pituitary-adrenal axis, cause Cushingoid features, and produce "sticky-chromosomes" in the male gonad. These examples of adverse effects warrant consideration when new drugs of this class are evaluated.

(ii) Drugs used to regulate mood and behavior. The adolescent is prone to psychosocial disturbances; the ambivalence created by his/her striving for self-identity and his/her dependent needs coupled with rapid changes in physiology and body form create a milieu of stress. Bizarre and unusual behavior may result when family interrelationships are strained or if school and peer interactions break down. Depression, anxiety, and acting out are common psychological symptoms which the physician is requested to control with drugs. There the problem of evaluating efficacy may be confounded by concurrent psychotherapy; this must be considered when adolescents are enrolled in a psychoactive drug study.

Effects on school performance, social behavior, and operation of vehicles should be kept in mind.

(iii) Drugs used for cosmetic purposes. Awakening interest in the opposite sex is characteristic of the adolescent. The adolescents' self-image in this context is related to their physical attractiveness. Minor skin blemishes may result in an inordinate expenditure of effort, time, and money to correct anything which may be considered a defect. At the same time, physiological changes make them susceptible to acne, seborrhea, and hirsutism. They seek and use a variety of medications, both on prescription and over-the-counter, to contend with these problems. Antibiotics, hormones, and vitamins may be prescribed for systemic use or topical application. Other medications (such as keratolytics, drying agents, and ointment powders to cover blemishes) are limited to external use.

For topically applied drugs, the problem of skin sensitization is superimposed on those of potential abuse and overdosage common to other classes of drugs.

5. **Ethics**

a. Informed consent should be obtained from the subject as a responsible individual, as well as from her/his parents.

b. The effects of drugs, even in the young adolescent, must include the possibility that females are pregnant and males may be fertile.

c. The possibility that the drug may have an effect on ova or spermatozoa must be considered.

6. Other - Compliance

Patients may fail to take the medication under study according to their protocol. This is particularly true of adolescent patients who are not yet mature enough to realize the need to take even the most important medications (i.e., insulin in juvenile-onset diabetes). Therefore, to evaluate drugs in this age group, methods to evaluate compliance will have to be devised and used.

III. SUMMARY OF REQUIRED STUDIES

The following summary is intended to list those studies which are felt to be required in all (or almost all) drugs to be approved for use in pregnant women, infants, and children. There will be exceptions. The recommendations are divided into two groups: animal studies and studies in pregnant women, infants, and children.

A. STUDIES IN ANIMALS

1. Chronic toxicity studies. This is the usual long-term multidose administration to two species, usually the rat and beagle dog. These studies should include effects on growth and skeletal maturation (bone age).
2. Appropriate methods for determining bioavailability using nonradiation-emitting techniques are to be developed. Initially "hot" methods for animal studies may serve as a prototype for the development of appropriate "cold" methods, but efforts should be directed to developing a sensitive "cold" method. The method(s) should be sensitive enough to measure with small sample size levels in serum expected to be in the therapeutic range. The method(s) should also differentiate the drug from its major metabolites. If the latter are pharmacologically active, additional techniques for these measurements are needed.
3. The pKa and lipid: water ratio of the chemical moiety used in the product should be determined.
4. Studies of absorption, distribution, metabolism, and excretion. These should account for a major percent of the administered dose and lead to formulation of a pattern of metabolism and disposition during both acute and chronic administration. Major metabolites should be identified. Unusual disposition -particularly in growing bone, teeth, or endocrine organs - which might be associated with adverse effects in the pediatric population should be sought.
5. The standard "3-phase" reproduction study.

B. STUDIES IN PREGNANT WOMEN, INFANTS, AND CHILDREN

The following factors are to be determined in each age group for which the drug will be approved. The usual sequence of testing should first involve teen-agers then successively younger children. Exceptions will occur when diseases are peculiar to one age group. The neonate must be approached with great care, since even studies in young children may not yield a reliable estimate of toxicity for the neonate. For studies of the fetus, infants treated as an inadvertent recipient by administration to the mother of a drug for a serious medical problem may be the first studies involving the fetus. Throughout the recommended studies that follow, there apparently are no important sex differences before puberty; thus, data obtained from both males and females may be pooled. This is a reasonable but still untested postulate, however.

1. Blood levels found with the range of doses adopted from studies in adults. If such studies have determined the therapeutic range, the dose required in infants and children to achieve this range must be an early priority.

2. Studies of absorption, distribution, metabolism, and excretion. The goals of such studies should include localization in tissues, rapidity of excretion, and time of peak onset.

   a. Absorption. The percent of a single and/or multiple dose that is absorbed should be determined.

   b. Distribution. Binding to plasma proteins at therapeutic blood levels should be determined. Studies of displacement of bilirubin from serum albumin are critical if the drug is to be used in neonates or late in pregnancy. If such displacement is found, additional studies with drugs which may be concurrently administered and the effect of pH, free fatty acids, etc., on the drug albumin-bilirubin complex are mandatory.

   c. Metabolism. Determination of the major biotransformation products, including a search for unique or unusual metabolites, may be coupled with studies of blood levels (No. 1). If significant age-related changes are found in metabolism, then a comparative profile of quantitative changes occurring with age may be necessary.

   d. Excretion. The fate of the drug, expressed either as percentage of the multiple daily dose or as single dose with an appropriate time scale as determined from the decline in serum levels or other monitor of excretion, should be ascertaind. Such studies should account for a major protion of the administered dose in most instances.

3. Bioavailability. If the dose form to be used in children is significantly different than that for adults, it must be considered as a new drug, and absorption and excretion studies should first be performed in adults. In any event, the dose form or forms used for pediatric patients must be used for studies of absorption in children. This stipulation will cover the potential problem of toxicity or influences of the vehicle or other components of the formulation.

4. Because of the multiple unique aspects of the neonate, a neonatologist should be part of the team which evaluates the influence of a new agent to which a fetus or a neonate has been exposed. Study must be made of possible interferences by the drug with metabolic reactions unique or of particular importance to neonates, such as the handling of bilirubin, glucose homeostaasis, acid-base balance, oxygen-carrying capacity, development of pulmonary surfactant, etc.

5. Depending upon the drug, consideration should be given to establishing a program for long-term follow-up of the offspring of women receiving the drug during pregnancy. Such studies need to evaluate both possible intra-uterine death and malformations. Since many malformations are not detected at birth, a program of follow-up should insure evaluation at least at 1 year of age. Malformations should include functional as well as anatomic abnormalities. Even longer follow-up is desirable, particularly for drugs which might be anticipated to have an adverse effect on neurologic development. However, the difficulties of such long-term studies are recognized and some compromise must be made. Depending upon the drug, similar but perhaps less intensive and extensive follow-up may be needed for children receiving the new drug during postnatal and later developmental stages.

6. For drugs which may be used chronically, the effects on weight gain, statural growth and skeletal maturation (including, perhaps, in some cases, serial bone age films), and sexual maturation should be assessed. The effects of chronic administration on behavior and learning are important areas, yet ones in which no exact requirements for studies can be delineated. The determination of effects on behavior and learning may be part of the evaluation of efficacy of psychoactive compounds; thus, indirectly, some data on safety will be obtained. However, in addition to specific benefical effects which will be observed, other areas demanding consideration are:

   a. classroom attentiveness and performance,
   b. grades, comments of teachers, etc.
   c. unusual or bizarre behavior,
   d. somnolence, depression, withdrawal,
   e. reports of trained observers, parents, teachers,
   f. formal testing procedures.

   In general, the longer the drug is to be administered the more important long-term follow-up becomes.

7. Studies of hematologic, hepatic, and renal damage from acute and chronic administration are needed because these organs are most readily affected by drugs, even if no toxicity has been demonstrated in adults. Such studies must be done with acute and chronic dosing.

8. Depending on the drug, specialized studies such as ECG, EEG, hearing, vision, etc. may be required. Certain clues can be taken from studies in adults and from the pharmacologic and chemical nature of the drug in determining the number and extent of such studies.

9. Before investigations are begun, provision must be made available for management and treatment of accidental or intentional overdosage and for severe toxic reactions to the drug.

10. Data must be obtained on the influence of the drug on fetal growth and differentiation for drugs which will be approved for pregnant women. Apgar scores, performance in the nursery, etc., are necessary parts of such studies. When appropriate, studies of addiction of the neonate and presence of withdrawal signs or symptoms must be performed or be in progress.

11. Concentrations of the drug and/or its metabolites in breast milk and effects on the nursing infant should be determined for drugs to be used in lactating women.

All recommendations made throughout these guidelines - and particularly in this summary section - must be viewed from the standpoint of flexibility, and appropriate modifications should be made for the individual drug, its indications for use, and the age of the patient for which it is intended.

The FDA guidelines also point out that drugs in the newborn infant can disrupt the myelinization process of the infant's brain and central nervous system. This is a physiologic process in which the nerve fibers are insulated with a fat-like substance called myelin. This insulation helps to assure that nerve impulses—the messages to and from the brain—will travel their normal routes.

Any alteration or disruption in the development of the intricately complex nerve circuitry of the human brain has the potential for permanently altering the way in which the nerve signals travel to and from the brain and the way in which the brain processes information.

What are the implications of these changes in the brain circuitry of the newborn infant? Dr. Donald Tower, Director of the National Institute of Neurological and Communicative Disorders and Stroke, recently stated in a speech before the National Committee for Research in Neurologic Disorders; "It is the biochemical circuitry—the biochemical messengers and relevant nerve cells in the brain—that form the basis for mankind's behavior."

Dr. Roberto Caldeyro-Barcia, a renowned scientist in perinatal medicine and immediate past president of the International Federation of Gynecologists and Obstetricians has cautioned:

> In the past 40 years many artificial practices have been introduced which have changed childbirth from a physiological event to a very complicated medical procedure in which all kinds of drugs are used and procedures carried out, sometimes unnecessarily, and many of them potentially damaging for the baby and even for the mother.

Despite the growing awareness that drugs administered to the mother can adversely affect the fetus, physicians continue to administer sedatives, tranquilizers, analgesics, regional anesthesia, uterine stimulants, and general anesthesia to women during childbirth, without advising them that none of the drugs have been subjected to a properly controlled, scientific evaluation and shown to be safe for the offspring. None of the methods currently accepted by the FDA and the medical community is an adequate test to evaluate the safety of obstetric-related drugs in regard to their effects on the long-term development of the exposed offspring. Recent research by Colletti and Nelson demonstrates that the FDA can no longer accept an Apgar score of 7 or over as an indication of infant well-being.

Epidural anesthesia during labor and birth is often referred to by anesthesiologists as the "Cadillac of anesthesia; yes, research now indicates that the effects of regional anesthesia on the exposed offspring are not as innocuous as anesthesiologists would have us believe.

A 6-week follow-up evaluation by Rosenblatt and colleagues of infants born to mothers who had bupivacaine epidurals demonstrated significant and consistent effects of bupivacaine throughout the 6-week assessment period. The initial effects of bupivacaine were cyanosis—a decreased oxygenation of the infant—and unresponsiveness. The infants' visual skills, alertness, mother organization, ability to control states of consciousness, and physiological response to stress were adversely affected throughout the 6-week testing period. The intensity of the effects tended to correlate with the concentration of the drug in the cord blood at birth.

Research by Brazelton has demonstrated that epidural anesthesia puts the infant at the same factor of risk for neurologic damage as if the child had been born to a mother who had been subjected to semistarvation during the first 7 months of her pregnancy. Data from England, yet to be published, shows that an infant born to a mother who has had an epidural block is 20 times more likely to be delivered by forceps. If the epidural block prolongs or disrupts labor, to the point where a cesarean section is required, the fetal brain is further jeopardized by the greater levels of maternal drugs necessary in such major surgery. There is not a single well-controlled study in this country that has looked at the effect of elective epidural anesthesia on the subsequent development of the need for cesarean section. I am talking about elective epidural. I think it is absolutely a disgrace that none of the Federal agencies have bothered to look at that possible correlation. As you probably know in some hospitals the cesarean section rate has risen to almost 30 percent.

Many of the drugs administered to the mother during labor and birth depress her central nervous system and can affect the fetus by lowering the mother's rate of respiration and her blood pressure. This combination of effects can interfere with the transfer of oxygen from the mother's circulatory system to the blood and brain of her unborn infant. The mother breathes in less oxygen, making less oxygen available to be absorbed by her blood. Because her blood pressure is slowed the end result is that a less than normal amount of oxygen reaches the baby at a less than normal rate of speed. There are drugs that can correct this problem but there is no guarantee that they will be effective soon enough to correct the likelihood of brain damage. Persistent fetal hypoxia (lowered oxygen saturation of the fetal blood) is considered by many scientists to be a greater threat to the fetal brain than is exposure to relatively short intervals of anoxia (complete cessation of oxygen). Research by Ucko in England found that children with normal IQ's who had been subjected to fetal hypoxia during labor tended to respond abnormally to stress.

The mother, too, can be harmed or injured by the drugs administered to her during childbirth. The package insert of the regional anesthetic Marcaine cautions the reader: "Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; peristent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery." I doubt whether women would be so anxious to have epidural anesthesia if they were allowed to read the insert.

The fact that the FDA has permitted the manufacturer to place this important warning in the section of the package insert entitled "Allergic Reactions," long after its inappropriate placement has been brought to the agency's attention, demonstrates the FDA's willingness to permit manufacturers to bury the most important information regarding drug risks in the less noticeable sections of the package inserts.

Although the FDA has never approved the use of oxytocin and prostaglandins for the elective stimulation of labor, these uterine stimulants are frequently administered to women during labor in order to augment their contraction and speed up their labors. For example, oxytocin is used in 25 percent of the labors in the State of New Jersey. One cannot possibly have 25 percent of the population having abnormal labor unless something is being done that is causing those abnormal labors.

Such augmentation can adversely affect the fetal brain by increasing intracranial pressure and by inhibiting the normal transfer of oxygen from the mother's circulatory system to the fetal brain. During a normal contraction the maternal blood vessels which carry oxygenated blood through the uterine wall are constricted. During this period of diminished blood flow the fetal brain is provided with a relatively constant supply of oxygen from oxygenated blood which has built up in the placenta's intervillous space during the resting intervals between contractions. These intervals between contractions are vital to the health of the fetal brain. Uterine stimulants which foreshorten these oxygen-replenishing intervals, by making the contractions too long, too strong, or too close together, increase the likelihood that brain cells will die. The situation is somewhat analogous to holding an infant under the surface of the water, allowing it to come to the surface to gasp for air but not to breathe.

It is not surprising that research by Colletti found a strong correlation between the administration of oxytocin during labor and subsequent learning disability in the offspring. She also found an even stronger correlation between the use of oxytocin and epidural and learning disability in the offspring.

While the risk of obstetric drugs can be decreased by careful fetal monitoring, research by Dr. Caldeyro-Barcia and his colleagues has demonstrated the increased risk of brain damage when the mother's membranes are artificially ruptured in order to screw the monitoring electrode into the fetal scalp.

Nature has provided protection for the fetal brain by encasing the infant in a fluid-filled amniotic sac—the "bag of waters". As long as the mother's membranes are intact the force of the uterine contractions is spread evenly over the entire surface of the infant. Amniotomy, the artificial rupture of the amniotic sac, can greatly increase intracranial pressure and cause a marked disalinement of the bones of the skull. This pressure and disalinement increase the likelihood that the membranes, which separate and support the various areas of the fetal brain, will be strained to the point of tearing, with subsequent hemorrhage within the brain. The artificial rupture of membranes has also been demonstrated in animals to increase the risk of fetal hypoxia or anoxia because of the increased possibility of cord compression and cord prolapse—the extrusion of the cord prior to the birth of the infant.

Caldeyro and his colleagues have urged repeatedly that the mother's membranes not be ruptured in order to speed up labor, or to screw electrodes into the fetal scalp for electronic monitoring, unless the mother's condition clearly indicates a medical need for such intervention.

Caldeyro-Barcia has pointed out in several of his presentations that subtle damage to the brain resulting from intracranial hemorrhage following amniotomy, forceps extractions, or vacuum extraction—conditions more frequently associated with the use of obstetric drugs—is not likely to become evident until the child reaches an age, around 8 or 9 years, when he or she will be called upon to use his or her more analytic skills, such as those involved in mathematics. This is especially important to be aware of because most of the studies on the effects of obstetric medication have been carried out for only 4 years or less. There has been no effort to look at the effects of these drugs on learning ability except the work by Dr. Brackbill and she will discuss her research later.

Many anesthesiologists have convinced themselves that obstetric drugs can actually protect the fetal brain by reducing the mother's discomfort or pain, when in fact these stresses have never been shown to cause hypoxia in the human fetus and infant. The research on which this hypothesis is based was done on wild monkeys. The researchers could not show a cause and effect relationship in tame monkeys. Yet women all over the country are being told that, if they suffer undue pain or stress in labor, their babies could possibly be brain damaged. This is obviously not true.

Potent pain relieving drugs can elevate the infant's cerebrospinal fluid pressure beyond the normal level. If there is brain swelling induced by intrauterine trauma, birth injury or pathophysiology, such drugs increase the possibility of brain damage. Drug-induced jaundice can adversely affect the newborn infant's brain by altering the normal biochemistry of its blood.

Drug-induced hypothermia, a condition whereby the infant cannot maintain its normal internal temperature, can cause brain injury in the newborn because the infant must use the oxygen needed to maintain the integrity of the brain, to turn its body "brown fat" into energy in order to maintain its normal internal temperature. Measures can be taken to reverse these drug-induced adverse effects, but there is no guarantee that such measures will be effective quickly enough to prevent permanent damage to the fetal brain.

Not all fetal trauma is the result of drugs or procedures. Caldeyro-Barcia, Flynn and others presented data at the 1979 Tokyo Congress of the International Federation of Gynecologists and Obstetricians which demonstrated that merely confining a mother to bed during labor tend to significantly: (a) prolong labor by 2½ hours; (b) increase the mother's need for pain-relieving drugs and uterine stimulants; (c) increase the need for forceps extraction of the infant; (d) increase the incidence of abnormal fetal heart rates and poor Apgar scores in the neonate. Until 3 years ago there was no hospital in the country that really was making an effort to carry out some of Caldeyro-Barcia plans in order to reduce the mother's need for obstetric drugs. His concepts are now being carried out at the North Central Bronx Hospital in New York City, a municipal hospital which the neonatologist tells me has 80 percent high-risk mothers—one of the highest risk populations in the country. There is no hospital in New York City that has a better infant outcome than the infants coming from the North Central Bronx Hospital. The midwives at North Central Bronx—and the program is essentially run by midwives—make every effort to avoid the need for drugs.

Behavioral scientists have found subtle brain damage to be far more prevalent among the general population than was once assumed. It is impossible to ignore the fact that drugs administered to the mother during labor and birth, and the procedures made necessary by such drug use, have the potential for adversely affecting the neurologic development of the exposed offspring, which may eventuate in failure to learn, failure in life and, for some, in criminal behavior.

Despite the FDA guidelines for the evaluation of drugs used in pregnant women, which clearly acknowledge the potential adverse effects of drugs trapped in the infant's brain at birth, the FDA has permitted manufacturers to imply that the major risk to the fetus occurs when the drug is taken by the mother during the first 3 or 4 months of her pregnancy. We found this type of restricted caution repeated in almost every package insert for obstetric drugs. None of the package inserts we read cautioned the reader that no properly controlled followup has been carried out on individuals exposed to the drug in utero and that, therefore, the drug may have delayed, long-term effects on the exposed offspring.

In preparing for these hearings we have carefully reviewed the text of the package inserts in the 1981 Physicians' Desk Reference for more than 50 prescription drugs known to be used in obstetrics in the United States. The list is not all inclusive, since it would be nearly impossible to determine which drugs are being used in all U.S. hospitals. But we have tried to review those drugs that are used relatively commonly.

While a substantial majority of the package inserts studied have a section entitled "Usage in Pregnancy," very few have any information on their use in obstetrics. In other words there is no section in the package insert entitled "Use During Labor and Delivery." As you will see from the table, entitled "Drugs Used in Obstetrics", which we submit for the record——

Mr. GORE. Without objection we will put that in the record.

[The information follows:]

DRUGS USED IN OBSTETRICS

(Keyed to 1981 Physicians' Desk Reference)

IMPORTANT NOTE: According to the Commissioner of the U.S. Food and Drug Administration, when the FDA has granted approval of a drug for use in: (a) pregnancy; (b) labor; (c) delivery; or (d) lactation, those conditions are specifically mentioned in the "Indications" section of the drug's package insert (see Column 6). He also confirmed that where there is no mention of such use under "Indications", the FDA has not approved use of the drug in those conditions. A "Usage in Pregnancy (or Obstetrics)" section in the package insert does not indicate that the drug has been approved by the FDA for that use.

Brand Name (Generic Name)	Action	1981 PDR page	Manufacturer	Package Insert Information Regarding Obstetric-Related Drugs						
				1 Safe use in pregnancy has not been established	2 Limits caution to fetal development	3 Focuses particularly on early pregnancy	4 Nonetheless, does not exclude use in labor and obstetrics	5 Safe use in pregnancy other than in labor has not been established	6 Labor and/or delivery listed in the "Indications" section	7 Other (see end page)
ADRENALIN (epinephrine)	VC	1323	PD	–	–	–	–	–	–	X
AMYTAL (amobarbital)	BA	1036	LY	X	–	–	–	–	–	Cat. B
ANECTINE (succinylcholine Cl)	MR	744	BW	X	X	X	–	–	–	–
ATARAX (hydroxyzine HCl)	TR	1535	RG	–	–	–	–	–	–	X
ATROPINE (atropine sulfate)	AC	1039	LY*	X	–	–	–	–	–	Cat. C
BENDECTIN (doxylamine succinate and pyridoxine HCl)	AN	1239 + Supp. A 32	MD	X	–	–	–	–	–	X
BLOCKAINE (propoxycaine)	RA	—	BR	Not listed in PDR						
BREVITAL (methohexital sodium)	IVA	1043	LY	X	X	–	–	–	–	–

(Continued on following pages)

KEY TO DRUG ACTION:

AA: Antacid
AC: Anticholenergic
AN: Antinauseant
BA: Barbiturate
CND: Central nervous system depressant

DI: Diuretic
ESH: Estrogen hormone
HY: Hypnotic
IA: Inhalation anesthesia
IVA: Intravenous anesthesia

LS: Lactation suppressant
MR: Muscle relaxant
NA: Narcotic (or narcotic-like)
NAA: Narcotic antagonist

PRH: Progesterone hormone
RA: Regional anesthesia
SD: Sedative
TR: Tranquilizer
US: Uterine stimulant
VC: Vasoconstrictor

© American Foundation for Maternal and Child Health, New York, 1981

8/13/81

DRUGS USED IN OBSTETRICS (Continued)

Brand Name (Generic name)	Action	1981 PDR page	Manufacturer	Package Insert Information Regarding Obstetric-Related Drugs						
				1 Safe use in pregnancy has not been established	2 Limits caution to fetal development	3 Focuses particularly on early pregnancy	4 Nonetheless, does not exclude use in labor and obstetrics	5 Safe use in pregnancy other than in labor has not been established	6 Labor and/or delivery listed in the "Indications" section	7 Other (see end page)
BUTISOL (sodium butabarbital)	BA	1115	McN	X	–	–	–	–	–	–
CARBOCAINE (mepivacaine HCl)	RA	682	BR	X	X	X	X	–	–	–
CITANEST (prilocaine HCl)	RA	592	AS	X	X	X	X	–	–	–
COMPAZINE (prochlorperazine)	TR AN	1672	SKF	X	–	–	–	–	–	–
DALMANE (flurazepam HCl)	TR HY	1496	RO	X	–	X	–	–	–	–
DELADUMONE (testosterone enanthate and estradiol valerate)	ESH	–	SQ	Listed but no information in PDR						
DELALUTIN (hydroxyprogesterone)	PRH	–	SQ	Listed but no information in PDR						
DEMEROL APAP (meperidine HCl)	NA	684	BR	X	X	–	X	X	–	–
DEMEROL (meperidine HCl)	NA	1899	WI	X	X	–	X	X	X	–
DIURIL (chlorothiazide sodium)	DI	1194	MSD	X	–	–	–	–	–	–
DURANEST (etidocaine HCl)	RA	594	AS	X	X	X	X	–	–	–
EDECRIN (ethacrynic acid)	DI	1196 + Supp. A 34	MSD	X	–	–	–	–	–	X
EMETROL (levulose, dextrose and orthophosphoric acid)	AN	1549	RR	–	–	–	–	–	–	–

9/13/81

DRUGS USED IN OBSTETRICS (Continued)

Brand Name (Generic name)	Action	1981 PDR page	Manufacturer	Package Insert Information Regarding Obstetric-Related Drugs						
				1 Safe use in pregnancy has not been established	2 Limits caution to fetal development	3 Focuses particularly on early pregnancy	4 Nonetheless, does not exclude use in labor and obstetrics	5 Safe use in pregnancy other than in labor has not been established	6 Labor and/or delivery listed in the "Indications" section	Other (use and page)
EPINEPHRINE (epinephrine)	VC	–	EN*	Listed but no information in PDR						
EQUANIL (meprobamate)	TR	1927	WY	Listed but no information in PDR						
ERGOTRATE (ergonovine maleate)	US	1063	LY	–	–	–	–	–	–	–
ETHER (diethyl ether)	IA	–	BA	Not listed in PDR						
FLUOTHANE (halothane)	IA	610	AY	X	X	X	–	–	–	–
GELUSIL (magnesium and aluminum hydroxides and simethicone)	AA	1352	PD	–	–	–	–	–	–	–
KETALAR (ketamine HCl)	IVA	1365	PD	X	–	–	–	–	–	X
LASIX (furosemide)	DI	938 Supp.* A 20	HR	X	–	–	–	–	–	Cat.C
LEVOPHED (norepinephrine bitartrate)	VC	691	BR	–	–	–	–	–	–	–
LIBRIUM (chlordiazepoxide HCl)	TR	1509	RO	X	–	X	–	–	–	–
LIDOCAINE (lidocaine HCl)	RA	531	AB*	X	X	X	X	–	–	–
LORFAN (levallorphan tartrate)	NAA	1511	RO	–	–	–	–	–	–	–

8/13/81

DRUGS USED IN OBSTETRICS (Continued)

Brand Name (Generic name)	Action	1981 PDR page	Manufacturer	Package Insert Information Regarding Obstetric-Related Drugs						
				1 Safe use in pregnancy has not been established	2 Limits caution to fetal development	3 Focuses particularly on early pregnancy	4 Nonetheless, does not exclude use in labor and obstetrics	5 Safe use in pregnancy other than in labor has not been established	6 Labor and/or delivery listed in the "Indications" section	7 Other (see end page)
LUMINAL (phenobarbital)	BA	—	WI	Listed but no information in PDR						
MAALOX (aluminum and magnesium hydroxides and simethicone)	AA	1580	RR	—	—	—	—	—	—	—
MAGNESIUM GLUCONATE (magnesium gluconate)	CND	1886	WR	—	—	—	—	—	—	—
MAGNESIUM SULFATE (magnesium sulfate)	CND	706	BR*	Listed but no information in PDR						
MARCAINE (bupivacaine HCl)	RA	692	BR	X	—	—	X	X	—	—
MEPERGAN (meperidine HCl and promethazine HCl)	NA	1937	WY	X	X	—	X	X	—	—
METHERGINE (methylergonovine maleate)	US	1577	SZ	—	—	—	—	—	X	X
METYCAINE (piperocaine)	RA	—	LY	Not listed in PDR						
MILTOWN (meprobamate)	TR	1871	WA	X	—	X	—	—	—	—
MORPHINE (morphine sulfate)	NA	874	ES*	Listed but no information in PDR						
MYLANTA (aluminum and magnesium hydroxides and simethicone)	AA	1759	ST	—	—	—	—	—	—	—
NARCAN (naloxone HCl)	NAA	881	EN	X	—	—	X	X	—	—

8/13/81

DRUGS USED IN OBSTETRICS (Continued)

Brand Name (Generic name)	Action	1981 PDR page	Manu- facturer	Package Insert Information Regarding Obstetric-Related Drugs						
				1 Safe use in pregnancy has not been established	2 Limits caution to fetal development	3 Focuses particularly on early pregnancy	4 Nonetheless, does not exclude use in labor and obstetrics	5 Safe use in pregnancy other than in labor has not been established	6 Labor and/ or delivery listed in the "Indications" section	7 Other (see end page)
NEMBUTAL (pentobarbital sodium)	RA	535	AB	X	X	X	X	–	–	–
NESACAINE (chloroprocaine HCl)	RA	1397	PW	X	X	X	X	–	–	–
NISENTIL (alphaprodine HCl)	NA	–	RO	Not listed in PDR						
NITROUS OXIDE (nitrous oxide)	IA	–	BA	Not listed in PDR						
NOCTEC (chloral hydrate)	SD	1720	SQ	X	–	–	–	–	–	Cat.C
NOVOCAIN (procaine HCl)	RA	695	BR	X	X	X	X	–	–	–
NUBAIN (nalbuphine HCl)	NA	881	EN	X	–	–	–	X	X	X
NUMORPHAN (oxymorphone HCl)	IA	882	EN	X	X	–	–	–	X	–
NUPERCAINE (dibucaine HCl)	RA	806	CB	–	–	–	–	–	–	–
PARLODEL (bromocriptine mesylate)	LS	1578	SZ	X	–	–	–	–	–	X
PENTHRANE (methoxyflurane, N.F.)	IA	563	AB	X	[illegible]	X	X	X	X	X
PENTOTHAL (thiopental sodium)	IVA	555	AB	X	–	–	–	–	–	Cat.C

8/11/81

DRUGS USED IN OBSTETRICS (Continued)

Brand Name (Generic name)	Action	1981 PDR page	Manufacturer	Package Insert Information Regarding Obstetric-Related Drugs						
				1 Safe use in pregnancy has not been established	2 Limits caution to fetal development	3 Focuses particularly on early pregnancy	4 Nonetheless, does not exclude use in labor and obstetrics	5 Safe use in pregnancy other than in labor has not been established	6 Labor and/or delivery listed in the "Indications" section	7 Other (see end page)
PHENERGAN (promethazine HCl)	AC	1946	WY	X	X	–	–	–	X	–
PITOCIN (oxytocin)	US	1381	PD	–	–	–	–	–	X	X
PLACIDYL (ethchlorvynol)	HY	568	AB	X	–	X	–	–	–	X
PONTOCAINE (tetracaine HCl)	RA	698	BR	–	–	–	–	–	–	–
SCOPOLAMINE (hyoscine hydrobromide)	AC	874	ES*	Listed but no information in PDR						
SECONAL (secobarbital sodium)	BA	1092	LY	X	–	–	–	–	–	Cat.B
SPARINE (promazine HCl)	TR	–	WY	Listed but no information in PDR						
SPARTOCIN (sparteine sulfate)	US	–	AY	Not listed in PDR						
STADOL (butorphanol tartrate)	NA	729	BL	X	–	–	X	X	X	X
SUBLIMAZE (fentanyl)	NA	956	JA	X	X	–	–	–	–	X
SUCOSTRIN (succinylcholine Cl)	MR	1739	SQ	X	X	X	–	–	–	–
SURITAL (thiamylal sodium)	BA	1387	PD	X	X	X	–	–	–	–
SYNTOCINON (oxytocin)	US	1582	SZ	–	–	–	–	–	X	X

8/13/81

DRUGS USED IN OBSTETRICS (Continued)

Brand Name (Generic name)	Action	1981 PDR page	Manufacturer	Package Insert Information Regarding Obstetric-Related Drugs						
				1 Safe use in pregnancy has not been established	2 Limits caution to fetal development	3 Focuses particularly on early pregnancy	4 Nonetheless, does not exclude use in labor and obstetrics	5 Safe use in pregnancy other than in labor has not been established	6 Labor and/ or delivery listed in the "Indications" portion	7 Other (see end page)
TALWIN (pentazocine lactate)	NA	1506	WI	X	–	–	X	X	–	X
THORAZINE (chlorpromazine)	TR	1691	SKF	X	–	–	–	–	–	X
TOCASAMINE (sparteine sulfate)	US	–	TR	Not listed in PDR						
TRILENE (trichlorethyline)	IA	–	BA	Not listed in PDR						
TUINAL (sodium amobarbital and sodium secobarbital)	BA	1097	LY	X	–	–	–	–	–	Cat.B X
VALIUM (diazepam)	TR	1530	RO	X	X	X	–	–	–	X
VISTARIL (hydroxyzine HCl)	TR	1422	PZ	–	–	–	–	–	X	X
XYLOCAINE (lidocaine HCl)	RA	595	AS *	X	X	X	X	–	–	–
YUTOPAR (ritodrine HCl)	MR	1259	MD	X	–	–	–	–	X	Cat.B X

KEY TO MANUFACTURER:

AB: Abbott
AS: Astra
AY: Ayerst
BA: Baker
BR: Breon
BL: Bristol
BW: Burroughs Wellcome
CB: Ciba
ES: Elkins-Sinn
EN: Endo
HR: Hoechst-Roussel
JA: Janssen
LY: Lilly
McN: McNeil
MD: Merrell-Dow
MSD: Merck Sharp & Dohme
PD: Parke-Davis
PW: Pennwalt
PF: Pfizer
RO: Roche
RG: Roerig
RR: Rorer
SZ: Sandoz
SKF: Smith Kline & French
SQ: Squibb
ST: Stuart
TR: Trent
WA: Wallace
WR: Western Research
WI: Winthrop
WY: Wyeth

* An asterisk added to manufacturer's symbol indicates additional sources of the drug

8/25/81

8. The FDA has established five pregnancy categories (A, B, C, D, X) to indicate a drug's potential for causing birth defects. The official explanation of these categories follows.

(Please note: Even drugs in Category A (the category of least risk, in which well-controlled studies in women have failed to demonstrate immediate risk to the fetus) have not been tested to determine whether or not there are delayed, long-term risks to the physical and neurologic development of the exposed offspring.

When a drug is designated as being in the FDA's Pregnancy Category B, there is no way one can tell from that designation whether or not well-controlled studies have been carried out in human mothers and their offspring and that the drug has been shown to have no adverse effects on offspring exposed to the drug in utero.)

(6) Pregnancy: This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) *Teratogenic effects.* Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(*a*) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: "Reproduction studies have been performed in (*kinds of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*)." The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*b*) *Pregnancy category B.* If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: "Pregnancy Category B. Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B. Reproduction studies in (*kind(s) of animal(s)*) have shown (*describe findings*) at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*c*) *Pregnancy category C.* If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*d*) *Pregnancy category D.* If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See 'Warnings' section." Under the "Warnings" section, the labeling states: "(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(*e*) *Pregnancy category X.* If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See 'Contraindications'

Ms. Haire. Most of these drug inserts indicate that safe use in pregnant women has not been established. However, a signifiant number of these inserts imply that, although safe use in pregnancy has not been established, safe use in labor has been demonstrated. They do this by stating that "safe use in pregnant women other than in labor has not been established." Or by the phrase "this does not exclude use in obstetrics" or similar language. Since the vast majority of drugs whose package inserts included such wording have not, in fact, been approved by the FDA as safe for use in labor and delivery, the inclusion of such statements or words is, in our view, deceptive and misleading and should be prohibited by the FDA.

We appreciate the fact that after many years of pressure from the women's health movement the FDA's drug regulations have been revised so that all drugs known to be used in labor and delivery, whether approved for that use or not, will eventually have a separate section in the package insert entitled "Usage in Labor and Delivery," which describes what is known and particularly what is not known about the effects of the drugs, when used in labor and delivery, on the long-term development of the child born of that delivery. For the manufacturer to continue to include such undocumented assurances of safety leaves the manufacturer vulnerable to future litigation if time proves the use of the product to have adverse effects on the mother's physiology and on the subsequent development of the exposed offspring.

While FDA officials and the pharmaceutical industry may say that FDA approval should not be considered the primary documentation of a drug's safety, the fact remains that, if the manufacturer could document the safety of his product's use, so as to obtain the FDA's approval of that use, then such approval would clearly enhance the sales of the drug for that purpose.

We have never suggested that physicians should not be free to use a drug for a non-FDA approved use. Nor have we asked that a drug be removed from the market, except for Bendectin. We do take the position that the health care professional and, in turn, the patient should be informed as to whether the intended use of the drug has or has not been approved by the FDA. We do not see how any responsible Federal agency or official can take a contrary position.

The women's health movement is keeping a close watch on drug labeling, drug advertising, and the FDA regulation of drugs that affect the lives of women and the lives of their families. Neither the FDA, the pharmaceutical industry, nor organized medicine can afford to continue to withhold information from the obstetric patient which she is entitled to have and the physician is obligated to provide her in order for her to make an informed decision as to whether to accept or forego the drugs offered her.

I submit as part of my testimony a copy of the pregnant patient's bill of rights, which includes an excellent definition of informed consent by the American College of Obstetricians and Gynecologists, and which reflects women's growing desire to be dealt with honestly regarding the risks of obstetric drugs and procedures.

[Material referred to follows:]

THE PREGNANT PATIENT'S BILL OF RIGHTS

THE PREGNANT PATIENT'S RESPONSIBILITIES

The International Childbirth Education Association (ICEA) is an interdisciplinary, volunteer organization representing groups and individuals who share a genuine interest in the goals of family-centered maternity care and education for the childbearing year.

ICEA constantly seeks to expand awareness of the rights and responsibilities of pregnant women and expectant parents. Most pregnant women are not aware of their rights or of the obstetrician's legal obligation to obtain their informed consent to treatment. The American College of Obstetricians and Gynecologists has made a commendable effort to clearly set forth the pregnant patient's right of informed consent in the following excerpts from pages 66 and 67 of its *Standards for Obstetric-Gynecologic Services*.

> "It is important to note the distinction between 'consent' and 'informed consent'. Many physicians, because they do not realize there is a difference, believe they are free from liability if the patient consents to treatment. This is not true. The physician may still be liable if the patient's consent was not informed. In addition, the usual consent obtained by a hospital does not in any way release the physician from his legal duty of obtaining an informed consent from his patient.
>
> "Most courts consider that the patient is 'informed' if the following information is given:
>
> - The processes contemplated by the physician as treatment, including whether the treatment is new or unusual.
> - The risks and hazards of the treatment.
> - The chances for recovery after treatment.
> - The necessity of the treatment.
> - The feasibility of alternative methods of treatment."
>
> "One point on which courts do agree is that explanations must be given in such a way that the patient understands them. A physician cannot claim as a defense that he explained the procedure to the patient when he knew the patient did not understand. The physician has a duty to act with due care under the circumstances; this means he must be sure the patient understands what she is told."
>
> "It should be emphasized that the following reasons are not sufficient to justify failure to inform:
>
> 1. That the patient may prefer not to be told the unpleasant possibilities regarding the treatment.
> 2. That full disclosure might suggest infinite dangers to a patient with an active imagination, thereby causing her to refuse treatment.
> 3. That the patient, on learning the risks involved, might rationally decline treatment. The right to decline is the specific fundamental right protected by the informed consent doctrine."

On the following pages ICEA sets forth the **Pregnant Patient's Bill of Rights**
along with the **Pregnant Patient's Responsibilities.**

THE PREGNANT PATIENT'S BILL OF RIGHTS

American parents are becoming increasingly aware that well-intentioned health professionals do not always have scientific data to support common American obstetrical practices and that many of these practices are carried out primarily because they are part of medical and hospital tradition. In the last forty years many artificial practices have been introduced which have changed childbirth from a physiological event to a very complicated medical procedure in which all kinds of drugs are used and procedures carried out, sometimes unnecessarily, and many of them potentially damaging for the baby and even for the mother. A growing body of research makes it alarmingly clear that every aspect of traditional American hospital care during labor and delivery must now be questioned as to its possible effect on the future well-being of both the obstetric patient and her unborn child.

One in every 35 children born in the United States today will eventually be diagnosed as retarded; in 75% of these cases there is no familial or genetic predisposing factor. One in every 10 to 17 children has been found to have some form of brain dysfunction or learning disability requiring special treatment. Such statistics are not confined to the lower socioeconomic group but cut across all segments of American society.

New concerns are being raised by childbearing women because no one knows what degree of oxygen depletion, head compression, or traction by forceps the unborn or newborn infant can tolerate before that child sustains permanent brain damage or dysfunction. The recent findings regarding the cancer-related drug diethylstilbestrol have alerted the public to the fact that neither the approval of a drug by the U.S. Food and Drug Administration nor the fact that a drug is prescribed by a physician serves as a guarantee that a drug or medication is safe for the mother or her unborn child. In fact, the American Academy of Pediatrics' Committee on Drugs has recently stated that there is no drug, whether prescription or over-the-counter remedy, which has been proven safe for the unborn child.

The Pregnant Patient has the right to participate in decisions involving her well-being and that of her unborn child, unless there is a clearcut medical emergency that prevents her participation. In addition to the rights set forth in the American Hospital Association's "Patient's Bill of Rights," (which has also been adopted by the New York City Department of Health) the Pregnant Patient, because she represents TWO patients rather than one, should be recognized as having the additional rights listed below.

1. *The Pregnant Patient has the right*, prior to the administration of any drug or procedure, to be informed by the health professional caring for her of any potential direct or indirect effects, risks or hazards to herself or her unborn or newborn infant which may result from the use of a drug or procedure prescribed for or administered to her during pregnancy, labor, birth or lactation.

2. *The Pregnant Patient has the right*, prior to the proposed therapy, to be informed, not only of the benefits, risks and hazards of the proposed therapy but also of known alternative therapy, such as available childbirth education classes which could help to prepare the Pregnant Patient physically and mentally to cope with the discomfort or stress of pregnancy and the experience of childbirth, thereby reducing or eliminating her need for drugs and obstertic intervention. She should be offered such information early in her pregnancy in order that she may make a reasoned decision.

3. *The Pregnant Patient has the right*, prior to the administration of any drug, to be informed by the health professional who is prescribing or administering the drug to her that any drug which she receives during pregnancy, labor and birth, no matter how or when the drug is taken or administered, may adversely affect her unborn baby, directly or indirectly, and that there is no drug or chemical which has been proven safe for the unborn child.

4. *The Pregnant Patient has the right* if Cesarean birth is anticipated, to be informed prior to the administration of any drug, and preferably prior to her hospitalization, that minimizing her and, in turn, her baby's intake of nonessential pre-operative medicine will benefit her baby.

5. *The Pregnant Patient has the right*, prior to the administration of a drug or procedure, to be informed of the areas of uncertainty if there is NO properly controlled follow-up research which has established the safety of the drug or procedure with regard to its direct and/or indirect effects on the physiological, mental and neurological development of the child exposed, via the mother, to the drug or procedure during pregnancy, labor, birth or lactation — (this would apply to virtually all drugs and the vast majority of obstetric procedures).

6. *The Pregnant Patient has the right*, prior to the administration of any drug, to be informed of the brand name and generic name of the drug in order that she may advise the health professional of any past adverse reaction to the drug.

7. *The Pregnant Patient has the right* to determine for herself, without pressure from her attendant, whether she will accept the risks inherent in the proposed therapy or refuse a drug or procedure.

8. *The Pregnant Patient has the right* to know the name and qualifications of the individual administering a medication or procedure to her during labor or birth.

9. *The Pregnant Patient has the right* to be informed, prior to the administration of any procedure, whether that procedure is being administered to her for her or her baby's benefit (medically indicated) or as an elective procedure (for convenience, teaching purposes or research).

10. *The Pregnant Patient has the right* to be accompanied during the stress of labor and birth by someone she cares for, and to whom she looks for emotional comfort and encouragement.

11. *The Pregnant Patient has the right* after appropriate medical consultation to choose a position for labor and for birth which is least stressful to her baby and to herself.

12. *The Obstetric Patient has the right* to have her baby cared for at her bedside if her baby is normal, and to feed her baby according to her baby's needs rather than according to the hospital regimen.

13. *The Obstetric Patient has the right* to be informed in writing of the name of the person who actually delivered her baby and the professional qualifications of that person. This information should also be on the birth certificate.

14. *The Obstetric Patient has the right* to be informed if there is any known or indicated aspect of her or her baby's care or condition which may cause her or her baby later difficulty or problems.

15. *The Obstetric Patient has the right* to have her and her baby's hospital medical records complete, accurate and legible and to have their records, including Nurses' Notes, retained by the hospital until the child reaches at least the age of majority, or, alternatively, to have the records offered to her before they are destroyed.

16. *The Obstetric Patient*, both during and after her hospital stay, has the right to have access to her complete hospital medical records, including Nurses' Notes, and to receive a copy upon payment of a reasonable fee and without incurring the expense of retaining an attorney.

It is the obstetric patient and her baby, not the health professional, who must sustain any trauma or injury resulting from the use of a drug or obstetric procedure. The observation of the rights listed above will not only permit the obstetric patient to participate in the decisions involving her and her baby's health care, but will help to protect the health professional and the hospital against litigation arising from resentment or misunderstanding on the part of the mother.

Prepared by Doris Haire, Chair., ICEA Committee on Health Law and Regulation

THE PREGNANT PATIENT'S RESPONSIBILITIES

In addition to understanding her rights the Pregnant Patient should also understand that she too has certain responsibilities. The Pregnant Patient's responsibilities include the following:

1. The Pregnant Patient is responsible for learning about the physical and psychological process of labor, birth and postpartum recovery. The better informed expectant parents are the better they will be able to participate in decisions concerning the planning of their care.
2. The Pregnant Patient is responsible for learning what comprises good prenatal and intranatal care and for making an effort to obtain the best care possible.
3. Expectant parents are responsible for knowing about those hospital policies and regulations which will affect their birth and postpartum experience.
4. The Pregnant Patient is responsible for arranging for a companion or support person (husband, mother, sister, friend, etc.) who will share in her plans for birth and who will accompany her during her labor and birth experience.
5. The Pregnant Patient is responsible for making her preferences known clearly to the health professionals involved in her case in a courteous and cooperative manner and for making mutually agreed-upon arrangements regarding maternity care alternatives with her physician and hospital in advance of labor.
6. Expectant parents are responsible for listening to their chosen physician or midwife with an open mind, just as they expect him or her to listen openly to them.
7. Once they have agreed to a course of health care, expectant parents are responsible, to the best of their ability, for seeing that the program is carried out in consultation with others with whom they have made the agreement.
8. The Pregnant Patient is responsible for obtaining information in advance regarding the approximate cost of her obstetric and hospital care.
9. The Pregnant Patient who intends to change her physician or hospital is responsible for notifying all concerned, well in advance of the birth if possible, and for informing both of her reasons for changing.
10. In all their interactions with medical and nursing personnel, the expectant parents should behave towards those caring for them with the same respect and consideration they themselves would like.
11. During the mother's hospital stay the mother is responsible for learning about her and her baby's continuing care after discharge from the hospital.
12. After birth, the parents should put into writing constructive comments and feelings of satisfaction and/or dissatisfaction with the care (nursing, medical and personal) they received. Good service to families in the future will be facilitated by those parents who take the time and responsibility to write letters expressing their feelings about the maternity care they received.

All the previous statements assume a normal birth and postpartum experience. Expectant parents should realize that, if complications develop in their cases, there will be an increased need to trust the expertise of the physician and hospital staff they have chosen. However, if problems occur, the childbearing woman still retains her responsibility for making informed decisions about her care or treatment and that of her baby. If she is incapable of assuming that responsibility because of her physical condition, her previously authorized companion or support person should assume responsibility for making informed decisions on her behalf.

Prepared by Members of ICEA

Published by International Childbirth Education Association, Inc.

For a complimentary copy send a stamped, self-addressed envelope to
Box 1900, New York, NY 10001

Bulk orders available from ICEA Publication/Distribution Center
P. O. Box 20048, Minneapolis, Minnesota 55420

There were three recent events which convinced me of the need to prepare my report on the FDA. The first occurred when I requested a list of those drugs approved by the FDA as safe for use in pregnancy and obstetrics and was told that the FDA has no system for retrieving such information from its records. I think that is unbelievable. It is also true for other conditions, not just obstetrics.

The second incident occurred when I learned that several key FDA officers were unaware that only those uses of the drug which appear in the "Indications" section of the drug's package insert are FDA-approved uses of the drug. Nor were those officers aware that only when the drug's use in pregnancy and/or obstetrics is noted in the "Indications" section of the package insert is the drug approved as safe for use in pregnancy and delivery.

When I called the FDA's Office of New Drug Labeling for information, Dr. Lloyd Millstein, the Director, informed me that the FDA had changed its requirement that only when an obstetric use is mentioned in the "Indications" section of the package insert was the drug approved by the FDA as safe for such use. He referred me to page 37465 of the June 26, 1979, issue of the Federal Register for confirmation of the change in requirements. However, I could see no notation in that text which canceled or modified the basic requirement. The correctness of my understanding has been confirmed by a recent letter from Commissioner Hayes which I submit for the record.

Mr. GORE. Without objection we will include that.

[The information follows:]

National
Women's Health
Network

Doris Haire, Chair
Committee on Health Law and Regulation
Return Address:
30 Beekman Place
New York, N. Y. 10022
Tel.: (212) 759-5510

May 7, 1981

Arthur Hayes, M.D., Commissioner
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Hayes,

It was a pleasure to meet you when you chaired your first consumer meeting at the FDA. I hope that you will find such meetings constructive. I was especially pleased that you confirmed my understanding that "only those uses mentioned in the "Indications" section of the drug's package insert are those uses which have been approved as safe by the FDA and that, in the case of pregnancy and parturition, unless the use of a drug in pregnancy, labor, birth and/or lactation is mentioned in the "Indications" section of the drug's package insert the drug has not been approved by the FDA". Your confirmation is consistent with that of former Commissioners Goyan and Kennedy.

Unfortunately, various officers of the FDA interpret the regulations differently. When I called Dr. Lloyd Millstein, head of the New Drug Labeling section, prior to the consumer meeting, he told me that the rules had been changed and sent me as confirmation a marked copy of the June 26, 1979 Federal Register (see enclosed page). I realize that the directive in the "Labor and Delivery" section is well intentioned, and its inclusion is an important improvement. However, it is equally important that the package insert clearly define those uses of the drug described in the text which have not been approved by the FDA as safe for such use. To omit this designation would lead many health professionals to the erroneous assumption that the drug has received FDA approval as safe for such use.

There are many health professionals who are apparently inadequately informed as to how to identify in the package insert an FDA-approved use of the drug from non-approved uses. Therefore, the National Women's Health Network requests that a notice be placed in the next FDA Bulletin, which reads:

> "HOW TO IDENTIFY FDA-APPROVED USES OF A DRUG
>
> Only those uses noted under the "Indications" section of the package insert have been approved as safe by the FDA. If, for example, the "Indications" section of the package insert does not specifically mention use of the drug during pregnancy, labor, delivery and/or lactation, the FDA has not approved of the drug as safe for such use."

Dr. Hayes May 7, 1981

While I realize that many health professionals are well aware of how to identify an FDA-approved use of a drug, obviously many do not. Such a notice will help to protect the health of the American public and is of sufficient importance to warrant its inclusion in a forthcoming FDA Bulletin.

I look forward to hearing from you in regard to this matter.

Best wishes,

Doris Haire
President

DBH/vs
Enclosure;
Federal Register page

section." Under "Contraindications," the labeling shall state: "*(Name of drug)* may *(can)* cause fetal harm when administered to a pregnant woman. *(Describe the human data and any pertinent animal data.) (Name of drug)* is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(ii) *Nonteratogenic effects.* Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) Labor and delivery: If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) Nursing mothers:

(i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: "Because of the potential for serious adverse reactions in nursing infants from *(name of drug)* (or, "Because of the potential for tumorigenicity shown for *(name of drug)* in *(animal or human)* studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "Caution should be exercised when *(name of drug)* is administered to a nursing woman."

(iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, "Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (*name of drug*) is administered to a nursing woman."

(9) Pediatric use: A specific pediatric indication, if any, shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage shall be stated under the "Dosage and Administration" section of the labeling. Statements on pediatric use of the drug for an indication approved for adults shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless this requirement is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter. If the requirements of § 314.111(a)(5)(ii) of this chapter cannot be met, this section of the labeling shall contain one of the following statements: "Safety and effectiveness in children have not been established," or "Safety and effectiveness in children below the age of ( ) have not been established." If use of the drug in premature or neonatal infants, or in older children, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling; or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection of the labeling shall refer to it.

(g) "Adverse Reactions": An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (*name of drug*) is (are) (*list reactions*). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (*list reactions*), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (*list reactions*)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of

FILMED FROM
BEST COPY AVAILABLE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 14 1981

Ms. Doris Haire
President, National Women's Health Network
30 Beekman Place
New York, New York 10022

Dear Ms. Haire:

Thank you for sending the comments in your letter of May 7, 1981, concerning prescription drug labeling and non-labeled indications (also referred to as "unapproved uses"). I want to apologize for the delayed response to your request that we inform health professionals, by means of an article in the Drug Bulletin, that only those uses listed in the Indications section of the package insert have been approved as safe by the FDA. I have reviewed this issue with people on my staff, and this review accounts in part for the delay. We have concluded that, while such a statement would be true in the technical sense, it would be misleading and--in many cases--not in the best interests of patients. Let me attempt to explain our thinking on this important and difficult question.

The issue of non-labeled indications has been widely publicized and was, in fact, the subject of an FDA Drug Bulletin article in October 1972 and of speeches and publications by FDA staff members and by the American Academy of Pediatrics' Committee on Drugs. (I have enclosed copies of these for your information.) We feel that health professionals are aware of the issue through these means, but we will continue to raise the issue periodically in order to assure that new members of the professions are made aware and that others are reminded. Specifically, I have arranged to have a proposal for an article on prescription drug labeling and non-labeled indications be submitted formally to the editorial board of the FDA Drug Bulletin .

Further, the uses listed in the Indications section of the package insert are those for which FDA has determined that there exists substantial evidence of effectiveness and for which a favorable benefit/risk judgment has been made. This does not mean that other unlisted indications may not have such evidence as well, but since there has been no determination about the safety and effectiveness for those indications, they are not included in the labeling.

I was pleased to note that you agree with FDA's requirement that, when a drug has a recognized use during pregnancy (whether or not such use is included in the Indications section) the labeling should provide available information on the effect of that drug on the mother and child and on labor and delivery. In effect, however, you ask that we make it clear that such use is not approved. As I mentioned above, labeling does not always contain all of the indications for which adequate data on safety and effectiveness exist. Furthermore, as Dr. Temple points out in his enclosed paper, "Legal Implications of the Package Insert," and as FDA has long held, "the physician must be free to use a drug for an indication or at a dosage not specified in the insert when such usage appears to be rational and for the benefit of the patient." In its paper, the AAP Committee on Drugs states that an "unapproved use" of a drug (i.e., one not in the labeling) "does not imply an improper use, and certainly not an illegal use. The word unapproved is merely to indicate lack of approval, not to imply disapproval or a contraindication based on positive evidence of lack of safety or efficacy."

I realize that you do not intend to indict a drug as being unsafe for an unlabeled use (unless, of course, such evidence exists). Rather, your aim is to inform the physician that a drug used for an indication not in the Indications section of the labeling may not have been shown to be safe for such use. For the reasons I mentioned above, however, I do not agree with your suggestion that the next FDA Drug Bulletin contain precisely the statement you recommend.

Two parts of the Labeling Regulation are pertinent to this discussion, and I want to call them to your attention.

1. Under the Indications section, the regulations state that if there is a common belief that a drug may be effective for a certain use but a preponderance of evidence shows that it is ineffective, FDA may require that the labeling so state. Although this deals with effectiveness, it is related as well to safety, because all drugs have side effects and because the benefit/risk ratio of a drug for an indication for which it is ineffective is unfavorable.

2. Under the Warnings section, the regulations state that the FDA may require a specific warning relating to a use not provided for under Indications when a drug is commonly prescribed for such use, when there is a lack of substantial evidence of effectiveness for that use, and when such usage is associated with serious risk or hazard. Let me assure you that a serious hazard from use of a drug would always be included in the labeling whether or not the drug is specifically indicated for the use in which the hazard has been observed.

Page 3 - Ms. Doris Haire

I hope that this explanation helps you understand why I cannot agree with your recommendation. I appreciate having your suggestions, however, for they gave me an opportunity to think through a number of provocative questions about the labeling of prescription drugs.

Sincerely yours,

Arthur Hull Hayes, Jr.

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs

Enclosures

1 - "Use of Drugs for Unapproved Indications: Your Legal Responsibility"; FDA Drug Bulletin; October 1972
2 - "Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the FDA"; Pediatrics; August 1978
3 - "Legal Implications of the Package Insert"; Primary Care; September 1974
4 - "Prescription Drug Advertising; Content and Format for Labeling of Human Prescription Drugs"; Federal Register; June 26, 1979

Ms. HAIRE. I have no doubt that Dr. Millstein truly believed that what he was saying was correct. That is probably what he was led to believe.

Shortly after his appointment as FDA Commissioner, I wrote to Dr. Hayes. I described the confusion expressed by various health professionals when I asked them how they identified an FDA-approved use of a drug. I requested that the FDA inform health professionals by means of an article in the FDA Drug Bulletin that only those uses listed in the "Indications" section of the package insert have been approved as safe by the FDA. The Commissioner's response was that "while such a statement would be true in the technical sense, it would be misleading—and in many cases—not in the best interests of patients."

Commissioner Hayes' position, that truthful information should be withheld from both health professionals and the public, illustrates the FDA's pattern of thinking which has made it so difficult for responsible consumer groups to work effectively with the agency. It is difficult to avoid the conclusion that the FDA is more interested in protecting the physician who prescribes the drugs than the patients who receive them.

It now appears that information regarding how to identify an FDA-approved use of a drug is being purposely withheld from the public. We could find no currently available FDA-printed information, book or pharmacopeia which instructs the reader as to how to identify an FDA-approved use of a drug. In refusing my request Dr. Hayes did say that such a notice was published in the FDA Drug Bulletin in 1972. One such notice in 10 years is hardly sufficient.

When I questioned obstetric nurses, midwives, supervisory personnel, graduating medical and pharmacy students, none were aware that only when the drug use in pregnancy and obstetrics is noted in the "Indications" section of the package is the drug approved by the FDA as safe for such use. Even the women who took my call to the FDA's Office of Consumer Affairs gave me an incorrect answer!

When I learned of the FDA's approval in 1979 of two powerful narcotic-like analgesics, Nubain and Stadol, as safe for use in obstetrics without first presenting evidence of safety to the FDA's Fertility and Maternal Health Drugs Advisory Committee for review, I realized that until Congressional and public attention was brought to bear on the inadequacies of the FDA's evaluation and regulation of drugs the agency would continue its laissez-faire approach to the evaluation of obstetric-related drugs. My exchange of letters with Dr. Marion Finkel, director of New Drug Evaluation, regarding Stadol demonstrates the FDA's laissez-faire approach. I submit this exchange of correspondence along with my testimony.

[The material referred to follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

MAR 4 1981

Doris Haire
American Foundation for Maternal
and Child Health, Incorporated
30 Beekman Place
New York, New York 10022

Dear Mrs. Haire:

Your letter of December 8, 1980 to the Commissioner concerning the use of butorphanol tartrate (Stadol) for the relief of prepartum pain has been referred to the Bureau of Drugs. Our response lists your questions for clarity.

1) What were the criteria for exclusion and inclusion used in establishing the safety of Stadol in regard to both the immediate and delayed, long-term effects of Stadol on the exposed offspring?

   There were no exclusion criteria for the offspring; all offspring of mothers participating in the investigation were studied.

2) What were the criteria used to determine the control group?

   a) Was the control group comprised of healthy unmedicated mothers and their offspring or mothers who had a different form of pharmacologic treatment for prepartum pain?

   The control group was determined by random allocation to treatment with the standard drug (meperidine). All women in this study received either the test drug or the comparison drug.

3) How many parturients and their offspring were included in the experimental group and how many were included in the control group?

   There were one hundred and forty patients in each group.

4) Who carried out the research to determine the immediate effects of Stadol on the exposed offspring?

   a) Has the research been published?
   b) In what refereed journal does it appear?

Dr. Albert Maduska of the Department of Anesthesiology at the University of Tennessee and Dr. Robert Hodgkinson at the University of Texas Medical Center, San Antonio, Texas performed the studies. There are two publications:

Maduska, A.L., Hajghassemali, M. A double-blind comparison of butorphanol and meperidine in labour: maternal pain relief and effect on the newborn. Can. Anesth. Soc. J. 25: 398-404, 1978.

Hodgkinson, R., Huff, R.W., Hayashi, R.H., Husain, F.J. Double-blind comparison of maternal analgesia and neonatal neurobehavior following intravenous butorphanol and meperidine. J. Int. Med. Res. 7: 224-230, 1979.

c) What methods of neurologic assessment of the newborn were used?

The evaluations that make up the APGAR score, the time interval from delivery to sustained respiration, and (in Dr. Hodgkinson's study only) a sixteen point neurological examination were used to assess the newborn.

5) Who carried out the research to determine the delayed, long-term effects of Stadol on the exposed offspring?

a) Has the research been published?
b) In what refereed journal does it appear?
c) What methods of neurologic assessment were used to evaluate the neurologic and physiologic state of the offspring?
d) At what ages were the neurologic assessments carried out?

No research on long-term effects of Stadol on the exposed offspring was done in these investigations. FDA is not aware of any evidence that treatment of labor pain with one or two doses of analgesic medication can result in long-term effects that are not mediated by immediate, clinically-observable, pharmacodynamic effects of the drug.

Maternal concerns:

1) When Stadol is administered intramuscularly (2 mg) or intravenously (1 mg) does Stadol:

a) Slow the parturient's gastrointestinal functioning?
b) Slow the transfer of oxygen from the parturient's bloodstream to that of her unborn infant?

Mrs. Doris Haire

We have no information on these points.

c) Cause uterine contractions to become dyscoordinate and, in turn, slow the progress of labor?
d) Increase the need for uterine stimulants during labor and delivery?

The data developed in the studies cited above indicated that there was no significant difference between the duration of labor in patients treated with Stadol and meperidine. Compared to meperidine, no increased need for uterine stimulants was found.

e) Inhibit the parturient's gag reflex?
f) Increase the possibility that a caesarean section will be needed to facilitate delivery?

There were no observations concerning the gag reflex. The incidence of caesarean sections was no higher in patients treated with Stadol than in patients treated with meperidine.

Fetal/Newborn Concerns:

1) When Stadol is administered intramuscularly (2 mg) or intravenously (1 mg) does Stadol cross the placenta and enter the fetal blood, brain, and other organs?

Stadol does cross the placenta and enter the fetal circulatory system. We may deduce from our knowledge of the physicochemical properties of the molecule that it subsequently enters the brain and other human organs. Animal studies show the drug to be distributed widely following injection.

2) Under what conditions does Stadol tend to accumulate in the fetal blood, brain, and other organs?

Cumulation of drugs occurs when the rate of delivery to a compartment (e.g., blood, brain, organs) exceeds the rate of removal from the compartment; multiple samples from each compartment are required to determine the rate of delivery and the rate of removal. There are ethical constraints on studies which require multiple blood samples from infants, and samples of brain and other organs have not been obtained in any human subjects.

Mrs. Doris Haire

3) What is the average lapsed time between the administration of Stadol to the parturient and the uptake of the drug by the fetal circulation?

We have no experimental data regarding this question, but it is likely that the transport of the drug to the fetus is very rapid.

4) What is the half-life of Stadol?

The half-life was not determined in parturient women. From information gained in other studies, the half-life following intramuscular injection is calculated to be about 2.7 hours.

5) What are the metabolites of Stadol and what effects do they have on the fetus and the newborn?

The major metabolite is the conjugate with glucuronide. It appears to be pharmacologically inactive.

6) Does Stadol administered to the parturient:

a) Slow fetal breathing movements?
b) Alter fetal heart rate patterns?
c) Lower blood gases in the fetus and newborn, and if so, how are they altered?

Any effect on fetal breathing movements is undoubtably dose-related. Direct observations on the fetus were not performed in these investigations. No differences in fetal heart rates between the two treatment groups were observed in these studies. Fetal blood gases were not monitored since this requires special methods for obtaining samples. There were no significant differences in the PCO_2 or pH of venous blood from the umbilical cords of babies born to mothers treated with Stadol or meperidine.

d) Alter neuronal maturation, cell differentiation, cell migration, and dendritic abortization in the brain of the fetus and newborn infant?

We have no information on this point, but we would not anticipate any effect following a brief exposure period.

e) Affect the infants' time to sustained respiration?
f) Increase the likelihood that the infant may require resuscitation?

Mrs. Doris Haire

In one investigation, infants of mothers treated with Stadol 2 mg I.M. had a shorter average time to sustained respiration than infants of mothers treated with meperidine 80 mg. None of the infants born to mothers treated with Stadol required resuscitation. We believe that overdosage could produce respiratory depression, but there have been no such incidents reported.

g) Affect the thermoregulation of the infant?
h) Affect the brain wave patterns of the fetus and newborn infant?
i) Affect the visual and auditory responses of the newborn infant?

These observations were not performed.

j) Cause the newborn infant's suckling to be incoordinate?

This was not directly evaluated in these studies, and there were no observations which suggested this effect.

7) What is the length of time Stadol tends to remain in the blood, brain, and other tissues of the infant after birth?

As mentioned above, determination of rates of drug removal would require multiple samples, and this has not been determined in infants or children. The half-life listed above was calculated from the results of studies in adults.

8) How long does Stadol appear in the mother's milk after birth?

We do not have exact information on this point. Based on half-life values, we would expect that there would not be any appreciative level in breast milk 24 hours after the maternal dosing was completed.

9) If the FDA does not have in its files properly controlled data which demonstrate the safety of Stadol in regard to the drug's delayed, long-term effects on the subsequent physical, neurologic, and mental development of the exposed offspring, why has FDA not required the package insert to caution the reader that the delayed, long-term effects of Stadol on human development are unknown?

Mrs. Doris Haire

As you know, the current prescription drug labeling regulations were published June 26, 1979. When fully implemented, the labeling for drugs with approved indications for use in obstetrics (also drugs with a recognized use in obstetrics, even if not approved for such use) will be required to provide under the Labor and Delivery section the available information concerning the long-term effects of the drug on the growth and neurological development of the child. If no information is available in this regard, the labeling shall state that fact.

The labeling for Stadol will be revised as necessary, in accord with the compliance schedule published May 16, 1980, a copy of which is enclosed for your information. You will note that the effective date for revised labeling for general analgesics (of which Stadol is a member) is May, 1983.

Dr. Zavadil has asked me to enclose the reprint requested in your telephone conversation with him on January 22, 1981.

Sincerely yours,

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

Attachments: (2)

American Foundation for Maternal and Child Health, Inc.
A Nonprofit Foundation for Interdisciplinary Research in Maternal and Child Health

30 Beekman Place, New York, N.Y. 10022
Telephone: (212) 759-5510

December 8, 1980

Officers & Trustees

Doris & John Haire, *Co-Presidents*
Ann C. Gray, *Vice President*
Peter A. M. Auld, M.D., *Trustee*
Ralph W. Gause, M.D., *Trustee*
Dorothea Lang, C.N.M., *Trustee*

Board of Consultants

James R. Allen, M.D.
George J. Annas, J.D.
David Banta, M.D.
John Boyce, M.D.
Ernest L. Boyer, Ph.D.
Yvonne Brackbill, Ph.D.
T. Berry Brazelton, M.D.
Roberto Caldeyro-Barcia, M.D.
Ann L. Clark, R.N.
Sanford N. Cohen, M.D.
Peter M. Dunn, M.D.
Avis J. Ericson, Pharm.D.
Emanuel A. Friedman, M.D.
Lawrence M. Gartner, M.D.
Arnold P. Gold, M.D.
Albert D. Haverkamp, M.D.
Reba Hill, M.D.
Derrick B. Jelliffe, M.D.
Marshall H. Klaus, M.D.
G. J. Kloosterman, M.D.
Irving Ladimer, S.J.D.
Michael Lewis, Ph.D.
Ashley Montagu, Ph.D.
Michael Newton, M.D.
Niles Newton, Ph.D.
Sir John Peel, M.D.
Lee Salk, Ph.D.
Sydney Segal, M.D.
Muriel Sugarman, M.D.
Myron E. Wegman, M.D.
Milton W. Werthmann, M.D.
William F. Windle, Ph.D.
Lucille Woodville, C.N.M.
Sumner Yaffe, M.D.

Jere E. Goyan, Ph.D., Commissioner
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Jere,

Because the FDA's approval of Stadol for the relief of prepartum pain (Sept. 1979) appears to represent the current thinking, attitudes, and objectives of the FDA, I would appreciate answers to the questions I have posed regarding Stadol and its effects on the parturient and her offspring.

I would like to call your attention to the following statements (underscoring added) made in the package insert of Stadol (see enclosed copy of PDR Supplement B/1980, Page B5):

> "Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.
>
> "Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.
>
> "Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.
>
> "Usage in Children: Safety and efficacy in children below 18 years have not been established at present."

While the text of the package insert of Stadol acknowledges that the drug can alter maternal blood pressure, heart rate, and respiration, there are many important questions left unanswered.

We would appreciate answers to the following questions, answers which we believe the FDA should have in order to justify FDA's approval of the drug Stadol as safe for use during labor:

1. What were the criteria for exclusion and inclusion used in establishing the safety of Stadol in regard to both the immediate and delayed, long-term effects of Stadol on the exposed offspring?

2. What were the criteria used to determine the control group?

   a) Was the control group comprised of healthy unmedicated mothers and their offspring or mothers who had had a different form of pharmacologic treatment for prepartum pain?

3. How many parturients and their offspring were included in the experimental group and how many were included in the control group?

4. Who carried out the research to determine the immediate effects of Stadol on the exposed offspring?

   a) Has the research been published?

   b) In what refereed journal does it appear?

   c) What methods of neurologic assessment of the newborn were used?

5. Who carried out the research to determine the delayed, long-term effects of Stadol on the exposed offspring?

   a) Has the research been published?

   b) In what refereed journal does it appear?

   c) What methods of neurologic assessment were used to evaluate the neurologic and physiologic state of the offspring?

   d) At what age were the neurologic assessments carried out?

MATERNAL CONCERNS:

1. When Stadol is administered intramuscularly (2 mg) or intravenously (1 mg) does Stadol:

   a) slow the parturient's gastrointestinal functioning?

   b) slow the transfer of oxygen from the parturient's bloodstream to that of her unborn infant?

   c) cause uterine contractions to become dyscoordinate and, in turn, slow the progress of labor?

d) increase the need for uterine stimulants during labor and delivery?

e) inhibit the parturient's gag reflex?

f) increase the possibility that a cesarean section will be needed to facilitate delivery?

FETAL AND NEWBORN CONCERNS:

1. When Stadol is administered intramuscularly (2 mg) or intravenously (1 mg) does Stadol cross the placenta and enter the fetal blood, brain, and other organs?

2. Under what conditions does Stadol tend to accumulate in the fetal blood, brain, and other organs?

3. What is the average lapsed time between the administration of Stadol to the parturient and the uptake of the drug by the fetal circulation?

4. What is the half-life of Stadol?

5. What are the metabolities of Stadol and what effects do they have on the fetus and newborn?

6. Does Stadol administered to the parturient:

   a) slow fetal breathing movements?

   b) alter fetal heart rate patterns?

   c) alter blood gases in the fetus and newborn, and if so, how are they altered?

   d) alter neuronal maturation, cell differentiation, cell migration, and dendritic arborization in the brain of the fetus and newborn infant?

   f) affect the newborn infant's time to sustained respiration?

   g) increase the likelihood that the infant may require resuscitation?

   h) affect the thermoregulation of the infant?

   i) alter the brainwave patterns of the fetus and newborn infant?

   j) affect the visual and auditory responses of the newborn infant?

   k) cause the newborn infant's suckling to be incoordinate?

7. What is the length of time Stadol tends to remain in the blood, brain, and other tissues of the infant after birth?

8. How long does Stadol appear in the mother's milk after birth?

9. If the FDA does not have in its files properly controlled data which demonstrates the safety of Stadol in regard to the drug's delayed, long-term effects on the subsequent physical, neurologic, and mental development of the exposed offspring, why has the FDA not required the package insert to caution the reader that the delayed, long-term effects of Stadol on human development are unknown?

The answers to the questions I have posed are essential to the safe care of both the childbearing woman and her offspring. I find it difficult to believe that the FDA could have approved the use of Stadol for prepartum pain without having the answers to the questions I have posed. I look forward to receiving your answers. I will share the information with other organizations which share my concern regarding the safety of obstetric-related drugs.

Sincerely yours,

Doris

Doris Haire
President

DBH/vs
Enclosure
PDR Supp. B/1980

Mr. HAIRE. The manufacturer of the drug Numorphan, approved by the FDA as safe for use in obstetrics in 1959, at a time when newborn evaluation was primitive at best, recently added obstetric use to the list of "Indications" in its package insert without having to clear such inclusion with the FDA. There is something basically wrong with such a system.

Dr. Finkel claims that the FDA has completed a careful review of the literature on obstetric-related drugs and found no reason to alter its present position in regard to how the FDA evaluates and regulates such drugs. I can only say that for the past 4 or 5 years I have attended essentially every meeting of the Anesthetic and Life Support Drug Advisory Committee and of the Fertility and Maternal Health Drugs Advisory Committee at which obstetric-related drugs were discussed. I have seen no evidence that an extensive review of obstetric-related drugs has been carried out by either of those committees. At one of the meetings three FDA staff members reviewed a few of the studies. In my opinion, their reports were very inadequate reviews of the scientific literature since none of the studies discussed included a drug-free control group. In addition, there was no evidence at that meeting that the members of the advisory committee had read the studies discussed.

In my presentation to the FDA's Anesthetic and Life Support Drug Advisory Committee I listed items of information which should be obtained from the manufacturer in order to make a considered evaluation of any drug. I submit this list as a part of my testimony this morning. None of the points of information which I feel are important to have in considering the safety of a drug for obstetric use was obtained for the drug Stadol.

[The material referred to follows:]

PROPOSALS FOR IMPROVED PROTECTION OF THE UNBORN CHILD

prepared by DORIS HAIRE

Chair, Committees on Health Law and Regulation of

The National Women's Health Network

The International Childbirth Education Association

President, American Foundation for Maternal and Child Health

FDA Anesthetic and Life Support Drug Advisory Committee

Subcommittee on Obstetrical Safety

February 19, 1980
Washington D.C.

PROPOSALS FOR IMPROVED PROTECTION OF THE UNBORN CHILD

by DORIS HAIRE

The FDA should immediately require that the manufacturer of every drug which the FDA has approved as safe for use during labor or delivery place a boxed precautionary statement regarding its use during labor and delivery in the package insert, label and promotional material for the drug. If no properly controlled investigation has been carried out to evaluate the delayed, long-term effects of the drug on the subsequent physical, neurologic and mental development of the offspring exposed to the drug in utero, then the very least the precautionary statement should advise the readers is as follows:

> "No properly controlled long-term follow-up has been carried out on individuals exposed to the effects of ______ in utero. There may be delayed, long-term, adverse effects on subsequent physical, neurologic and mental development which cannot be determined at this time."
>
> "Physicians are not required to report an adverse drug reaction to the FDA; therefore, there is no way of determining the exact rate of adverse drug reactions to ______ when used in non-research obstetric care."
>
> "Since even the short-term direct and indirect effects of this drug vary with the individual physiology of each mother and her unborn child, the term "overdose" as it applies to the fetus cannot be defined for this drug."

LS

If the drug has not been approved by the FDA for use in pregnancy and obstetrics then the package insert should state in bold type

> "This drug has not been approved by the FDA for use in pregnancy, parturition or lactation." *

If the FDA is to carry out its charge to protect the American public, and especially the unborn child because it is so vulnerable, from drug-induced injury then the text of the package insert must reflect the state of knowledge regarding that drug. For drugs used in obstetrics this is especially important since there are two patients, not one. While the drug may benefit the mother, it may have an adverse effect on the immediate or long-term well being of the unborn infant.

To protect the mother and her unborn child from drug-induced injury the FDA has a duty to provide the physician and, in turn, the mother, with information in the package insert regarding:

1. the average lapsed time between the administration of the drug to the pregnant or parturient woman and the uptake of the drug by the fetal circulation, according to the quantity and the route of administration.
2. how long the drug will remain in the blood, brain and other tissues of the infant after birth.
3. how long the drug will appear in the mother's breast milk.
4. the date the FDA first released or approved the product for marketing.
5. the date the information in the package insert was last reviewed and approved by the FDA.

* If the drug has been approved by the FDA for use in pregnancy, parturition and/or lactation the section of the package insert entitled "Indications" should contain a statement:
"This drug has been approved by the FDA for use during ______________________________
(pregnancy, parturition and/or lactation
described in the section concerned with ______________________________
(pregnancy, parturition and/or lactation)

6. the references on the clinical research which the manufacturer submitted to the FDA to support the manufacturer's contentions of safety.
7. A statement "This drug has not been approved by the FDA for use in pregnancy, parturition and/or lactation.", when that is the case.

The package insert should inform the physician and, in turn, the mother if there is a possibility that the drug will:

1. slow maternal respiration
2. slow fetal breathing movements
3. alter maternal heart rate
4. alter the fetal heart rate patterns
5. lower the mother's blood pressure
6. slow gastro-intestinal functioning
7. slow the transfer of oxygen from the mother's bloodstream to that of her unborn infant.
8. alter the other blood gases in the fetus and newborn infant
9. alter neuronal maturation, cell differentiation, cell migration and dendritic arborization in the brain of the fetus and newborn infant.
10. cause uterine contractions to become incoordinated and, in turn, slow the progress of labor.
11. increase the need for uterine stimulants during labor and delivery.
12. inhibit the mother's gag reflex and therefore increase the possibility of aspiration of vomitus.
13. Increase the possibility that fundal pressure, episiotomy, forceps extraction, vacuum extraction or cesarean section will be needed to facilitate delivery.

14. necessitate the need for electronic or ultrasonic fetal monitoring.

The package insert must inform the physician and, in turn, the mother if use of the drug increases the possibility that:

1. the infant's time to sustained respiration will be delayed
2. the infant may require resuscitation
3. the thermoregulation of the infant will be adversely affected
4. the brain wave patterns of the fetus and infant will be altered
5. the visual and auditory responses of the newborn infant will be inhibited
6. the infant's suckling will be incoordinate.

The package insert should also state whether the drug increases the possibility that the mother will sustain:

1. temporary or permanent bowel incontinence or urinary incontinence
2. neurologic shut down
3. loss of perineal sensation, or any other temporary or permanent disability

The FDA states in its guidelines, General Considerations for the Clinical Evaluation of Drugs in Infants and Children, that the "higher risk potential inherent in (newborn infants) dictates the most substantial evidence of benefit to be derived from the use of a new drug." The women's health movement believes that this same caution applies to old drugs, currently being used in obstetrics — none of which have been proven safe for the unborn child and most of which have never been approved by the FDA for use in pregnancy or obstetrics. (According to Dr. Martha Freeman, Assistant to the Associate Director for New Drug Evaluation, only those drugs which contain a specific indication for pregnancy or obstetric use under the section "Indications" of the package insert, have been approved for that use by the FDA. We have been able to identify only nine such drugs). The guidelines go on to say that "Evaluation at delivery usually detects only gross anatomical malformations."

If the FDA is to fulfill its charge as public protector then the Agency must require that all investigators use as the control group an adequate number of healthy unmedicated mothers and their offspring to serve as a baseline against which to measure subtle, as well as gross deviations from normal newborn infant behavior and response and later development.

It is not in the interests of the unborn infant to depend on electronic fetal monitoring alone to evaluate the effect of obstetric drugs on the infant. FDA officers have recently cautioned:

> "Increasing concern has arisen regarding the fetal safety of widely used diagnostic ultrasound in obstetrics. Animal studies have been reported to reveal delayed neuromuscular development, altered emotional behavior, EEG changes, anomalies and decreased survival. Genetic alterations have also been demonstrated in in-vitro systems."

For more detailed information regarding FDA's position on ultrasound used in obstetrics see "Diagnostic Ultrasound Equipment", Federal Register, Part III, February 13, 1979.

Amniotomy (the artificial rupture of membranes) which is frequently carried out in order to screw the monitoring electrodes into the fetal scalp is a procedure which has been shown by Caldeyro-Barcia, Gabbe and others to increase the risk of umbilical cord compression, cord prolapse, and increased pressure on the fetal brain. Amniotomy causes the baby's head, rather than the intact amniotic wedge, to serve as a battering ram to open up the birth canal.

I recently attended the Tokyo Congress of the International Federation of Gynecologists and Obstetricians. The research data presented by Doctors Caldeyro-Barcia, Flynn and others demonstrated that merely confining a mother to bed during labor tends to significantly:

(a) prolong labor (by 2½ hours)

(b) increase the mother's need for pain relieving drugs and uterine stimulants

(c) increase the need for forceps extraction of the infant

(d) increase the incidence of abnormal fetal heart rates and poor Apgar scores in the neonate

Research by Hoult demonstrated a 5-fold greater incidence of forceps delivery among women who are administered epidural anesthesia and that permitting the epidural to wear off during the end of the first stage of labor did not significantly improve the incidence of spontaneous birth.

Drugs are frequently used as a substitute for quality care because health professionals have been led to believe that the drugs actually protect the fetal brain from damage.

The research by Myers, while interesting, cannot be used to justify obstetric medication as beneficial to the fetus. Myers' extensive review of the literature describes the many studies carried out in monkeys which demonstrate that when a wild monkey, experiencing contractions, is purposely frightened and inflicted with pain, the adrenal medulla of the monkey produces an excess of hormones called catecholamines. The catecholamines and sympathetic nerve reaction cause the blood vessels of the uterus to constrict, causing hypoxia (oxygen deprivation) in the fetus. The authors are careful to point out that this cause and effect has not been shown to be true in humans. Unfortunately, the authors did not mention that such cause and effect had not been shown to occur in tame monkeys who were accustomed to human contact. The cautious reader will discern from the Myers review and from the research of others working in that area of research, the very important fact that the discomfort and intermittent pain of undrugged labor and birth have not been shown to cause an increase in maternal catecholamines nor a sympathetic nerve reaction sufficient to cause hypoxia in the human fetus.

We do not contend that drugs should be denied women during labor and birth. We do contend that women have a right to know, and the physician has a legal obligation to inform the mother, of the risks involved in obstetric-related drugs.

OBSTETRIC OUTCOME AT THE NORTH CENTRAL BRONX HOSPITAL
NEW YORK CITY

It is appropriate to this discussion to describe the obstetric service of the North Central Bronx Hospital because it is a so-called "city hospital" serving one of the more sociologically depressed areas of New York — probably a more depressed area than any found in Washington, Chicago or Detroit.

The mothers cared for at North Central Bronx Hospital are primarily black and Hispanic, with a smattering of whites. Thirty percent (30%) of the mothers are clearly medically high-risk. An additional equal percentage of mothers would probably be considered "at-risk" in most institutions.

The care of mothers who are high-risk and at-risk is provided by midwives and essentially is the same as that care provided to low-risk mothers unless there is a medical indication for intervention. If an infant is anticipated to be sick, premature, small-for-dates etc. , a third year pediatric resident and a resident assistant is present for the delivery. A neonatologist is available at all times.

Seventy percent (70%) of the mothers receive no drugs during labor and delivery. Strong emotional support by both the mother's chosen companions and the midwifery staff, and ambulation of the patient during the first stage of labor significantly reduces the need for drugs.

A review of the records of approximately 2,608 births carried out during 1979 at the North Central Bronx Hospital reveals the following enviable statistics:

* Approximately 90% of the deliveries were normal, spontaneous vaginal deliveries (without fundal pressure).

* 93% of the infants over 1,000 grams had Apgar scores of 7 or above at 1 minute of life, and at 5 minutes the rate was 98.3%.

* The incidence of instrumental delivery was 2.34%: low-forceps 1.57%; mid-forceps 0.5%; vacuum extractor 0.15%.

* The neonatal mortality rate among infants 1,000 grams or over was 4.2 per 1,000; at 750 grams or over it was 7.6.

* The perinatal mortality rate among infants 750 grams or over was 14.5. (Statistics not available for 1,000 grams +).

* The overall Cesarean section rate was 9.0% (7% primary and 2% repeat)

* All mothers who had experienced a previous Cesarean section were allowed to experience spontaneous labor. Of these, 37% gave birth vaginally.

* There were no elective inductions of labor.

* Uterine stimulants such as oxytocin, were employed in only 3% of mothers' labors and only when there was a medical indication.

* Great care is taken by the midwives to avoid the inadvertent or intentional rupture of the mother's membranes during internal examinations of the mother during labor.

* Vaginal examinations are kept to a minimum during labor in order to avoid causing the mother unnecessary discomfort, to avoid the inadvertent rupture of the mother's membranes, and to avoid an increased likelihood of maternal infection.

* Fewer than 50% of mothers (including the 30% who were high-risk) were monitored electronically. Many of the mothers are monitored only intermittently in order to minimize the fetus's exposure to the potential risks of ultrasound.

- Mothers who are not high-risk are allowed to eat and drink during labor. This practice has not resulted in a single case of aspiration of vomitus in the two years since the institution of the practice.
- The mother's pelvis and perineum are not "prepped" (shaved and washed with an antiseptic solution). Enemas are not given.
- Throughout their labor and birth mothers are accompanied by one or two companions of their choosing.
- 64% of the mothers gave birth in their labor beds in the labor rooms. 21% gave birth in their labor beds which had been moved to the delivery room because of an indication that the mother might need an assisted delivery or that the assistance of a pediatrician might be required. In only 15% of births were mothers moved to the delivery table for birth.
- 85% of mothers gave birth in the semi-sitting position without stirrups.
- Almost half (45%) of the mothers gave birth over an intact perineum. Episiotomy was performed in only 26% of births. 26% of the mothers experienced 1st or 2nd degree tears. Most 1st degree tears did not require sutures and all healed without complication.
- Premature and small-for-dates infants are delivered over an intact perineum if there is sufficient stretch to the perineum to avoid trauma to the fetal head.

Experience gained in the obstetric service of the North Central Bronx Hospital demonstrates that including in the investigation of a drug a control group comprised of low-risk, at-risk and high-risk mothers who received no drugs whatsoever during labor and delivery, is not only essential to the proper evaluation of the drug's effects on the mother and her infant but also appears to be, in general, in their best interests.

Mr. HAIRE. Despite our repeated requests that the FDA establish a multidisciplined Perinatal Drug Advisory Committee, the agency has refused on the grounds that there were insufficient funds. Neither the FDA's Fertility and Maternal Health Drugs nor the Anesthetic and Life Support Drug Advisory Committees has the necessary expertise to evaluate the effects of obstetric drugs on the subsequent development of the exposed offspring. No behavioral scientists regularly attend their meetings.

For years the FDA has taken the illogical position that it is all right to give childbearing women drugs which have not been proven safe for the unborn infant but not all right to carry out a followup on the exposed infants in order to determine the latent effects of those drugs on the offspring. For years I have been trying to figure out how they can justify this position.

Understandably, neither the FDA nor obstetricians can be expected to be eager to have the latent effects of obstetric drugs on the exposed offspring carefully examined by behavioral scientists. Scientists who apply to the various Federal agencies for funding of such research have consistently had the research approved but unfunded. That is a standard type of approval. It is a way of camouflaging disapproval.

Scientists tend to accept rejection of such research proposals without complaint, since to raise the ire of the Federal grant givers may result in subsequent rejections for future, less threatening research proposals.

If respected scientists do manage to secure funding to investigate the latent effects of obstetric-related drugs on the offspring, it is extremely difficult, and at times impossible, to get their research published. Needless to say, medical journals are reluctant to publish research which points a finger at members of the profession.

The research by Drs. Brackbill and Broman, which has demonstrated that obstetric drugs can adversely affect the subsequent development of the offspring is still being withheld from the public more than 2 years after it should have been released by the National Institute of Neurological and Communicative Disorders and Stroke. The Brackbill-Broman study might never have been completed had it not been for women in the health movement who pressed NINCDS to process the data on obstetric drugs.

Several years ago I questioned the NINCDS office responsible for the collaborative perinatal program as to why no effort had been made to investigate the effects of obstetric drugs on the subsequent physical and neurological development of the exposed offspring, I was told that such an evaluation would cost $350,000 and was considered not worth the money. I suggested that in light of the $150 millions already spent on the project the additional sum could be justified.

There are 4 million children and youths (1 out of every 10) in the United States so severely neurologically or emotionally handicapped that they require special education and training. The majority of impaired children, including those with cerebral palsy, were born within the normal range of gestational age and birth weight. There is a tremendous amount of research funding of programs that are looking into prematurity, low birth weight, and other high-risk conditions.

Yet, in reviewing the annual reports of the various Federal agencies concerned with maternal and child health we could find no record of well-controlled research being funded which investigated the delayed, long-term effects of obstetric-related drugs on the subsequent neurologic development of the exposed offspring. It almost appears as if the Washington agencies are hesitant to find research which examines the effects of obstetric drugs on the neurological development in the offspring because they are afraid of what they might find.

The former chairman of the American Academy of Pediatrics' Committee on Fetus and Newborn, who was asked by the academy to comment on the General Accounting Office's 1979 report on the FDA, made a statement which he later was unable to support with scientific documentation. His undocumented statement read: "Maternal apprehension and pain can have a serious effect on the fetus; in these cases, medication for pain relief is essential."

The reluctance of many pediatricians to call attention to the deficit of research and to caution women about the inherent risks of drugs offered to them by their obstetricians may be due, in part, to the fact that most pediatricians depend on obstetricians to refer newborn infants as new patients. A constant flow of new patients is necessary to maintain a pediatric practice, since older teenage patients move on to other physicians.

A second reason for this reluctance to caution women about the inherent risk of obstetric drugs may be the fact that pediatricians also prescribe drugs for children which have not been approved by the FDA as safe for that use. I regret to say the women's health movement has begun to feel that pediatricians are guilty by silence. There is a great amount of antagonism toward obstetricians by women today. I think if pediatricians continue to be so quiet knowing what they know, that this antagonism will spread.

The FDA Consumer magazine, prepared and published by the FDA, frequently withholds from the public information on the serious side effects, risks, and pertinent areas of uncertainty regarding the drugs and devices discussed in articles which appear in that publication. Two recent articles which discussed drugs used in pregnancy and obstetrics suggested that the effect of a drug on the fetus and newborn was primarily associated with the quantity of the drug and the frequency of administration.

You will see from my paper "Physiochemical Factors and the Pharmacokinetics of Obstetrics Related Drugs" which was prepared with the help of Drs. Sumner Yaffe and Sanford Cohen and which I submit for the record, that there are several factors which can affect the way a drug taken by or administered to a pregnant or parturient woman can affect the immediate well being and the long-term development of the child.

[The material referred to follows:]

PHYSIOCHEMICAL FACTORS AND THE PHARMACOKINETICS OF OBSTETRIC RELATED DRUGS

The effects of a drug or medication taken by or administered to a pregnant or parturient woman on the immediate well-being and long-term development of the child exposed to the drug in utero can be affected by several physiochemical, pharmacodynamic factors. Some of these factors are:

(a) the size of the pregnant or parturient woman

(b) the condition of the pregnant or parturient woman - whether she is anemic or diabetic, is deficient in protein, has liver or kidney damage, inherited a metabolic disorder or enzyme deficiency, etc.

(c) the condition of the fetus - whether he is premature or has been undernourished in utero, has inherited a metabolic disorder or enzyme deficiency, is subject to Rh incompatibility, etc.

(d) whether it is a single or multiple pregnancy

(e) the condition of the placenta - aging characteristics, pathology, size, perfusion rate and amount, etc.

(f) the time the drug is taken or administered relative to conception, fetal development, labor or birth

(g) the quantity of the drug ingested or administered and whether it is given in single or repeated doses

(h) the route of administration of the drug

(i) the absorption characteristics of the drug

(j) the distribution of the drug within the mother, placenta, amniotic fluid and fetus

(k) the rate of placental diffusion of the drug and the maternal-fetal ratio reached

(l) the rate and ability of metabolism and excretion of the drug by the mother

(m) the rate and ability of metabolism and excretion of the drug by the fetus and the rate at which the drug is returned to the mother

(n) the pH (acid-base balance) of the fetal-placental-maternal system

Physiochemical factors and the pharmacokinetics of obstetric related drugs (cont.)

(o) **the concentration of the drug or its metabolites left within the circulation and tissues of the infant when he is detached from his mother's circulatory system at birth**

(p) **the rate and ability of metabolism and excretion of the drug by the newborn infant as affected by environmental factors such as temperature, nursery procedures, drugs administered postnatally, etc.**

When one considers the difficulty of predicting the effects of a single drug on fetal metabolism, distribution, retention and excretion, it becomes readily apparent that it is almost impossible to predict the effects of combination drugs on the child exposed to the drugs in utero.

Prepared by Doris Haire, President, American Foundation for Maternal and Child Health;
Chair, Committee on Health Law and Regulation of the
National Women's Health Network

In addition to a drug's direct action on the mother and fetus, there is the risk of the drug acting synergistically with other drugs and obstetric stresses, increasing the drug's adverse effects on the fetus and newborn.

Because of our past ignorance drugs have become the primary treatment, rather than the backup treatment for alleviating the mother's discomfort or pain during labor and birth.

As mentioned earlier, several research programs have shown that encouraging the mother to walk, stand, and sit during labor tends to reduce the expectant mothers's need for drugs. In the majority of cases, ambulation has been shown to reduce the mother's discomfort or pain, reduce her need for uterine stimulants, lessen the likehood of abnormal fetal heart rates, shorten labor, reduce the need for forceps extraction, and improve the status of the infant at birth. Despite these findings the majority of women in the U.S. are still confined to bed during labor, administered drugs, and hooked up to a fetal monitor. None of these practices has been shown to be in the best interests of the vast majority of women and their infants.

Such persistence in continuing the practice of routinely drugging women in labor is made all the more irresponsible by the fact that no one knows the delayed, long-term effects on the child of rupturing the mother's membranes, a procedure which is required in order to screw the monitoring electrodes into the baby's scalp. I emphasize the word "screw" because health professionals often tell the mother that the electrode will be "attached" without explaining how the electrode is attached. I sometimes feel we should ask those doctors who minimize the discomfort such an electrode can cause the infant to sit for their boards with a monitor screwed into their scalps.

Nor do we know the long-term effects of irradiating the fetus with diagnostic levels of ultrasound used in fetal imagery [sonogram] and for monitoring the fetal heart rate.

Research in animals indicates that rupturing the mother's membranes in order to screw the electrodes into the fetal scalp increases the likelihood of umbilical cord compression and subsequent fetal hypoxia. The FDA has expressed its concern to health professionals that animal studies have been reported to reveal that diagnostic levels of ultrasound cause a delay in neuromuscular development, altered emotional behavior, EEG changes, anomalies and decreased survival.

Yet the FDA has not made a significant effort to call this information to the public's attention or, more importantly, to require manufacturers of electronic fetal monitoring devices to provide prospective mothers with printed information which advises the mother of these findings. To my knowledge, Roche, which produces one of the monitors, is the only company that has a statement that says the long-term effects of this practice of ultrasound are unknown. It is in small print and in the back of the booklet. We feel FDA should require all monitoring device companies to provide the patient with a package insert or information leaflet that talks about the possible long-term effects or at least talks about the risks of uncertainty.

We do not know whether ultrasound will be the DES of the next generation. It will take at least 20 years before we know. The effect of ultrasound on the ova of the female offspring will take even longer to ascertain.

Women have a right to know and the FDA has an obligation to advise the public that there are inherent risks to the use of obstetric drugs and devices even though they are approved for that use and regulated by the FDA. It is the position of the National Women's Health Network that if a Federal agency approves a drug or device as safe for use in obstetrics without requiring the manufacturer to provide the prospective mother with printed information which includes a discussion of the immediate risks and the areas of uncertainty regarding the product's delayed, long-term effects on the exposed offspring, then the Federal Government must also be held responsible for the care and compensation of those individuals injured or harmed by that drug or device.

The National Women's Health Network has several suggestions for legislation which would improve the performance of the FDA and other Federal agencies responsible for various aspects of maternal and child health. We submit the following recommendations as part of our statement before this hearing.

Mr. GORE. Without objection we will include those recommendations in the record at this point.

[The information follows:]

LEGISLATIVE RECOMMENDATIONS OF THE NATIONAL WOMEN'S HEALTH NETWORK

1. Make the FDA and its procedures and policies more open and accountable to the public. (Such openness and accountability has been recommended by the HEW Review Panel on New Drug Evaluation in 1977, the U. S. General Accounting Office in 1979, and the Joint Commission on Prescription Drug Use in 1980.)

2. Require patient package inserts (or drug information leaflets) for all drugs. (The exclusion of certain drugs from the requirements should not be the prerogative of the FDA.)

3. Require the manufacturer of an FDA-regulated drug to:

   (a) File with the FDA all adverse drug reaction inquiries, as well as reports, received from health professionals and consumers;

   (b) Carry out a systematic, long-term follow-up of individuals exposed to the drug;

   (c) Institute a system of periodic review of drug effects once the drug is on the market;

   (d) Accurately report his findings to the FDA.

4. Require the FDA to:

   (a) List in the drug's package insert and any patient information leaflets the name and address of the FDA division regulating that specific drug;

(b) Include the following cautionary statements when such statements apply to a particular drug:

> No well-controlled, long-term follow-up has been carried out on individuals exposed in utero to the effects of this drug. There may be delayed, long-term, adverse effects on subsequent physical, neurological, and mental development which cannot be determined at this time.
>
> Physicians are not required to report an adverse drug reaction to the FDA; therefore, there is no way of determining the exact rate of adverse drug reactions to this drug when used in non-research obstetric care.
>
> Since even the short-term direct and indirect effects of this drug vary with the individual physiology of each mother and her unborn child, the term "overdose", as it applies to the fetus, cannot be defined for this drug.

(c) Establish an 800 telephone number which would allow the public to receive information as to how to submit a written, adverse reaction report to the FDA.

5. Create a National Commission on Maternal and Child Health, to be headed by a behavioral scientist who is knowledgeable in the areas of neurologic dysfunction, obstetrics, newborn care, and human development. In addition to health professionals with a wide range of expertise, a balance of knowledgeable consumer representatives should serve on the commission.

6. Require all hospitals receiving Federal funds of any kind to:

   (a) Use a nationally uniform birth record, developed by the U.S. Department of Health and Human Services, which can be keyed to the child's education and death records. Such records, devoid of the patient's name, shall become available to the Department for research purposes.

(b) Institute a Drug Utilization Review Committee to audit the use of drugs.

7. Create and fund a new Collaborative Perinatal Study.

This study should be carried out in a relatively short period of time (one month) to insure an entusiasm for accurate record-keeping and should be under the direction of the Nation Commission for Maternal and Child Health (as earlier described). To avoid the major flaw of the earlier Collaborative Perinatal Project (1959-1965) the study should include a control group of healthy, unmedicated mothers and their offspring to serve as a baseline against which to measure deviations in human behavior and development.

8. Require all states receiving Federal monies for health care services to have a law or regulation which:

   a) Requires hospitals to preserve the mother's complete medical records with those of the newborn infant until that child reaches the age of 24, or older, and to make these records available to those in the behavioral, health, and education sciences authorized by the mother to review the records;

b) Provides for patient access to their own hospital medical records and the right to copy their records for a reasonable fee. Nineteen (19) states currently have such laws (see attached chart).

c) Assure the patient's right to informed consent, as has been done by New York State (see attached Public Health Law 2503).

9. Establish a Division of Midwifery within the Department of Health and Human Services for the purposes of facilitating the expansion of midwifery services in the U. S., monitoring the education and care provided by licensed and certified nurse-midwives, and monitoring the education and care provided by the rapidly increasing number of lay midwives in the U. S.

10. Require that each state receiving Federal monies for health care services have legislation mandating direct third-party payment for obstetric services provided by midwives qualified to practice by national certification, state licensure, or local authority. The Federal government has set a precedent by providing direct third-party payment to qualified midwives in its Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Regulation 6010.8-R.

11. Require all states receiving Federal monies for health care services to have a statute which would require hospitals with obstetric units to provide staff privileges to all midwives qualified to practice by national certification, state licensure, or local authority, and to provide the same obstetric back-up presently provided for obstetric residents and junior staff. Such a statute would reduce the number of women seeking obstetric care from lay midwives unqualified to provide such care.

12. Protect those health professionals and employees of Federal health care facilities who report injurious or potentially injurious care, abondonment, and/or overcharges, or who refuse to witness a fraudulent consent form from dismissal or other penalties meted out by the employer or the facility in which they practice.

13. Require all Federal agencies to hold open public meetings twice yearly, with time allotted for public questions and comments; this would go far to reduce some of the waste in research funding and bring Federal research funding more in line with public concerns.

Many of the above recommendations regarding the FDA appear in the brief I submitted to the FDA in 1973, a copy of which I submit for the record. In that brief I document the FDA's ability to correct many shortcomings without the need for new legislation.

STATE OF NEW YORK

13104

IN ASSEMBLY

June 12, 1978

Introduced by COMMITTEE ON RULES—(at request of M. of A. Butler)—read once and referred to the Committee on Health

AN ACT to amend the public health law, in relation to furnishing information to an expectant mother with respect to drugs to be used by the attending nurse-midwife

The People of the State of New York, represented in Senate and Assembly, do enact as follows:

Section 1. Section twenty-five hundred three of the public health law, as added by senate bill no. 8154, relating to furnishing drug information to expectant mothers, is hereby amended to read as follows:

§ 2503. Drug information to be furnished expectant mothers. The physician *or nurse-midwife* to be in attendance at the birth of a child shall inform the expectant mother, in advance of the birth, of the drugs that such physician *or nurse-midwife* expects to employ during pregnancy and of the obstetrical and other drugs that such physician *or nurse-midwife* expects to employ at birth and of the possible effects of such drugs on the child and mother.

§ 2. This act shall take effect on the same date as senate bill no. 8154, relating to furnishing drug information to expectant mothers.

STATE REGULATIONS REGARDING THE PRESERVATION OF HOSPITAL MEDICAL RECORDS FOR VOLUNTARY OR NON-PROFIT HOSPITALS*

	No. years adult hospital records must be preserved	No. years nurses' notes must be preserved	No. of years newborn's records must be preserved	Must nursery nurses' notes be preserved with newborn's records	Must labor/delivery record be preserved with newborn's records	Do patients have access to their hospital records
Alabama	22	0	22	No	Yes	No
Alaska	7	7	20	No	Yes	Yes
Arizona	3	3	3	Yes	Yes	No
Arkansas	10	10	28	Yes	No	No
California	7	7	19	Yes	No	No
Colorado	10	10	28	Yes	Yes	Yes
Connecticut	25	25	25	Yes	No	Yes
Delaware	2	2	26	No	No	No
Dist. of Col.	10	10	10	Yes	Yes	No
Florida	0	0	0	No	No	Yes
Georgia	6	6	24	Yes	No	No
Hawaii	0	0	0	No	No	No
Idaho	7	7	28	No	Yes	No
Illinois	0	0	0	No	No	Yes
Indiana	7	7	7	No	No	Yes
Iowa	0	0	0	No	No	No
Kansas	10	10	19	Yes	Yes	No
Kentucky	5	5	23	Yes	No	No
Louisiana	6	6	6	Yes	Yes	Yes
Maine	0	0	0	No	No	Yes
Maryland	3	0	3	No	No	No
Massachusetts	30	30	30	No	Yes	Yes
Michigan	0	0	0	No	No	Yes
Minnesota	Permanently	Permanently	Permanently	Yes	Yes	Yes
Mississippi	10	Varies	28	No	Yes	No

*This information was compiled by Doris Haire, President, American Foundation for Maternal and Child Health, New York, N.Y., 1980.

	No. years adult hospital records must be preserved	No. years nurses' notes must be preserved	No. of years newborn's records must be preserved	Must nursery nurses' notes be preserved with newborn's records	Must labor/delivery records be preserved with newborn's records	Do patients have access to their hospital records
Missouri	0	0	0	No	No	Yes
Montana	25	5	25	Yes	No	No
Nebraska	10	10	22	No	Yes	No
Nevada	3	0	25	Yes	No	Yes
New Hampshire	7	0	25	No	No	No
New Jersey	10	10	23	Yes	Yes	Yes
New Mexico	10	0	19	No	No	No
New York	6	0	24	Yes	No	No
No. Carolina	25	25	25	Yes	Yes	No
No. Dakota	25	7	25	Yes	No	No
Ohio	2	2	2	No	No	Yes
Oklahoma	3	0	3	Yes	No	Yes
Oregon	25	25	25	Yes	No	Yes
Pennsylvania	15	15	25	No	No	Yes
Rhode Island	5	5	23	Yes	Yes	No
So. Carolina	10	10	25	Yes	Yes	No
So. Dakota	0	0	0	No	No	Yes
Tennessee	10	10	19	No	No	No
Texas	0	0	0	No	No	No
Utah	10	10	25	Yes	Yes	No
Vermont	10	25	10	Yes	Yes	No
Virginia	5	5	23	No	Yes	Yes
Washington	10	10	21	Yes	No	No
West Virginia	0	0	0	No	No	No
Wisconsin	0	0	0	No	No	Yes
Wyoming	25	25	25	No	Yes	No

Ms. HAIRE. There are several things we would like to see come from this hearing. First patient package inserts for all obstetric related drugs. In the package inserts we would like to see that each drug is identified as having been approved or not approved for use in obstetrics by FDA. The FDA has begun to categorize drugs according to fetal risk as in Pregnancy Category A, B, D, C, and X. None of the categories, including category A, assures safety for the exposed offspring. Category B is particularly misleading because no one can tell from that designation whether or not well-controlled studies in humans have shown no adverse effects on the offspring. I called Dr. Millstein, head of FDA's New Drug Labeling, and asked him if he could tell me from a drug's designation as Pregnancy Category B whether well-controlled human studies have been carried out to evaluate the safety of the drug in regard to the offspring. He said no.

We would like to see that every woman is taught the importance of asking her obstetrician and her pediatrician for a copy of the package insert of all drugs prescribed for her and the members of her family and reading the package insert, especially the "Indications" section, before the drug is taken. Such precaution should be observed by the public in general but is particularly important for pregnant women and breast-feeding mothers. This does not mean that the pregnant woman should necessarily refuse to take a drug that has not been approved by the FDA for that use. My report, "How the FDA Determines the 'Safety' in Drugs—Just How Safe Is 'Safe'?" which I completed in preparation for this hearing, represents more than a decade of probing and observations.

In 1973 I presented a brief to the FDA entitled "Proposals for Improved Protection of the Unborn Child." Many of the recommendations that I have made in my presentation today came directly from that 1973 brief. Most of the recommendations I have made do not require legislation. They really just take a new direction on the part of FDA. With his wife as a health educator I think Dr. Hayes has an understanding of what I am talking about. I hope to see that changes are made within the FDA. I would like to work with FDA, not against it. I have made every effort to do so and hope to do so in the future.

[The brief referred to follows:]

Proposals for Improved Protection of the Unborn Child by the U. S. Food and Drug Administration

November 1973

Presented by:

Doris Haire, President
American Foundation for Maternal and
Child Health, Inc.
Chairwoman, Committee on Health Law and
Regulation, International Childbirth
Education Association

The FDA, Drugs and the Childbearing Woman

The U. S. Food and Drug Administration (FDA) has failed to use its statutory authority to adequately protect the American consumer, and in particular the unborn child, from the possible adverse effects of FDA sanctioned[1] or approved[2] drugs.

By failing to use its statutory authority the FDA has allowed millions of childbearing women and their unborn children to be exposed to prescription and non-prescription drugs, chemicals and devices which the FDA has sanctioned or approved for use or sale without requiring the manufacturers to show proof that their products will not adversely affect the physical, neurological and mental development of the unborn child and future adult. While the FDA has met the specific requirement of the law that the proposed product must meet the claims of the manufacturer, the FDA has not gone beyond this to inquire as to matters not covered by the basic claims of the manufacturer. Evidently the FDA has limited its concern to the short term effects of the product, and primarily the effects on the mother alone, even though it is evident from numerous studies that the unborn child may be affected, both short term and long term, by the product.

---

[1] For purposes of this paper a "sanctioned" drug or device is one which the FDA cleared for sale or use prior to the 1962 amendments to the Food, Drug and Cosmetics Act (the Act), U.S.C.A. Sec. 301 et seq. Clearance by the FDA of such products required little more than a filing of a registration statement, followed by a waiting period. If no objections were brought against the use of the product during the waiting period the FDA approved or sanctioned the product for sale or use, essentially on the basis of relative safety.

[2] For purposes of this paper an "approved" drug or device is one which the FDA approved for sale or use after the 1962 amendments to the Act for effectiveness, as well as safety, based on premarket determinations offered by the manufacturer.

Not only has the FDA approved unproven[3] drugs, chemicals and devices for use by pregnant, parturient and lactating women, but the FDA has compounded this problem by failing to require all manufacturers to adequately warn the physicians and/or users, via package insert sheets, promotional material, advertising media and such pharmacologic guides as the Physicians Desk Reference (PDR) when their products have not been proven safe for the unborn child.

The fact that the FDA has no official pharmacologic guide such as the PDR, Modern Drug Encyclopedia, etc., which would offer unbiased information regarding drugs and devices, is a detriment to the American consumer. For example, many potentially dangerous drugs, such as spartein sulfate, a drug used to initiate or stimulate labor, are not listed in the PDR, a commonly used information resource for health professionals.

Congress has granted the FDA various powers under the 1938 Food, Drug and Cosmetics Act[4] (the Act) and its subsequent amendments to protect the public. These powers include:

- The power to police the contents of drug labeling, including package inserts.[5]

---

[3] For purposes of this paper an "unproven" drug or device is one which is sanctioned or approved by the FDA but one which has not been proven safe as to its long term effects on the development of the child.

[4] U.S.C.A. Sec. 301 et seq.

[5] Act Sec. 502, 21 U.S.C.A. Sec. 352. The Act exampts dispensation to the patient of prescription drugs from many of the labeling requirements, Sec. 503(b), 21 U.S.C.A. Sec. 353(b), but the provisions of Sec. 705(b), 21 U.S.C.A. Sec. 375(b), concerning dissemination of emergency information, seem to overcome this exemption in many circumstances, as will be discussed throughout this paper.

- The power to police and set standards for the contents of drug advertising.[6]

- The power to cause dissemination of information to the public in order to prevent imminent dangers to the public health and gross deception of the consumer.[7]

It is our view that the general public has been and is being deceived as to the safety of drugs without adequate knowledge of the possible hazards inherent in drugs and devices now sanctioned or approved for sale or use by the FDA by pregnant, parturient and lactating women.

With regard to drugs introduced since May 1, 1963, the effective date of the 1962 amendments to the Act[8], the FDA has additional powers concerning both pre and post marketing testing and the dissemination of information.[9] Unfortunately the vast majority of drugs and devices employed in the care of pregnant, parturient and lactating women were "sanctioned" for sale or use prior to the 1962 amendment and were not subject to the present FDA standards.

---

[6] Act Sec. 502(n), 21 U.S.C.A. Sec. 352(n). It should be noted that the FDA may also require preclearance of advertising in extra-ordinary circumstances.

[7] Act Sec. 705(b), 21 U.S.C.A. Sec. 375(b). It is clear that this provision can be used to overcome many of the provisions discussed in note (2), supra. The FDA itself has defined an imminent danger to the public health:

> "(a) Within the meaning of the ... Act... an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The "imminent hazard" may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an "imminent hazard" of such occurrence exists."
>
> "(b) In exercising his judgment on whether an "imminent hazard" exists, the Commission will consider the number of injuries anticipated and the nature, severity and duration of the anticipated injury." (21 CFR Sec. 3.73).

[8] P.L. 87-781; (1962).

While we realize the past contribution of the FDA we are disturbed by the fact that even our present regulations allow massive unmonitored experimentation with human lives and mental potential which is not ~~even subject to~~ in keeping with the Nuremberg Code.[10] The uninformed general public is being used to establish the long term safety of a product, rather than using a limited number of subjects who are fully aware that the long term effects of the product under investigation are unknown. Furthermore the public is being used in this way without scientifically valid sequential evaluations of the children exposed to the drugs, so that it is doubtful that useful information will ever emerge from such "experiments".

The FDA has failed in its charge to protect the American consumer and the unborn child in several ways:

1. The FDA does not now, nor has it ever required clinical proof that a drug or device offered for use by pregnant or parturient women is safe as to its short term and long term effects on the physical, neurological

---

[9] Act Sec. 505, 21 U.S.C.A. Sec. 355 governs the approval and marketing of new drugs.

[10] The Nuremberg Code specifies that the experimental subject should be informed of "all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment."

and mental development of the fetus or child before the FDA sanctions or approves the product for sale or general use by childbearing women.

The FDA presently requires pre-clinical animal testing before approving new drugs. Such testing must "give proper attention to the conditions of use recommended in the proposed labeling such as, for example, whether the drug is...to be used in...pregnant women or women of childbearing potential."[11] Since there is no animal which duplicates human physiology, tests on animals (or aborted fetuses) cannot be accepted as "conclusive evidence" of the short term and long term effects of a drug or device on the child. (Those drugs sanctioned by the FDA for marketing or use prior to 1963 were not even subject to this limited testing.)

2. Except in the area of approved new drugs, where such action is mandated by statute[12], the FDA does not require that the manufacturer carry out systematic follow-up information-gathering in order to evaluate the long-term effects of drugs.[13]

3. The FDA permits manufacturers to issue information in the package insert sheets which is obsolete and to use language which is frequently evasive and

---

[11] 21 C.F.R. 130.4(d).

[12] Act Secs. 505(e), 505(j), 21 U.S.C.A. Secs. 355(e), 355(j).

[13] See Buday, The Package Insert: Significance, Style and Synthesis, 22 Food, Drug & Cosmetic L.J. 547 (1968); Simmons, FDA Looks At The Package Insert, 27 Food, Drug & Cosmetic L.J. 117 (1972)

often misleading in describing the known hazards and possible complications which can result from the use of the drug or device.[14]

4. By not requiring a manufacturer of a drug or device to include a clear warning that a product sold over-the-counter has not been proven safe for the unborn child, and by not using its emergency powers to provide such information in the case of prescription drugs,[15] the FDA has allowed the manufacturer to delude the consumer into assuming that the product has been proved safe for the unborn child, since it has been approved by the FDA.

5. The FDA does not require the manufacturer to warn the user of the more obtuse but pertinent facts about a given medication and its effect on the fetus whenever administered to the pregnant or parturient woman. For example, drug induced uterine inertia may precipitate the need for amniotomy, a procedure whereby the amniotic membranes are ruptured in order to speed up labor. Yet, research by Caldeyro-Barcia, President Elect of

---

[14] See Simmons, supra at 121. He quotes at length from the final report of the Commissioner of the National Research Council's Drug Efficiency Study, which cites biased, out-of-date, and unfactual material in package inserts as well as vague, insufficient and irrelevant information, saying much of it would not have withstood factual review at the time it was written.

[15] Over-the-counter drugs are required to bear adequate directions for use, i.e. directions as to how a drug can be used safely, 21 C.F.R. 1.106(a). Under this directive many such drugs bear warnings to pregnant women but do not necessarily warn of possible dangers to the unborn child, unless the FDA has so directed. Prescription drugs bear no such warning unless the physician directs it.

the International Federation of Gynecologists and Obstetricians, and his co-workers indicates that rupturing the amniotic sac may, in itself, create hazards to the unborn child.[16]

Xylocaine, and other similar drugs, when used as regional anesthesia tend to immobilize the lower portion of the mother's body, which in turn, increases the likelihood that the normal progress of labor will be slowed, spontaneous birth may be inhibited, and that birth must be assisted by fundal pressure or forceps extraction — procedures which can in themselves be hazardous to the child. Yet when one reads the package insert sheet no such warnings are evident.

6. The FDA's inaction has further allowed the manufacturer to mislead the physician and the user by permitting the omission of cautionary statements from promotional material and reminder advertisements.[17]

As a consequence of the FDA's inaction health professionals and parents have tended to grow complacent about the use of medications by obstetric patients. As a result few American babies are products of a drug-free biologically normal pregnancy and birth. Because of the FDA's failure to act millions of American unborn children have been exposed to drugs in utero which have been sanctioned or approved by the FDA — nausea remedies, diuretics, laxatives, appetite suppressants, antispasmatics, labor stimulants, sedatives, tranquilizers, muscle relaxants, amnesiacs, narcotics, analgesics, regional anesthesias and inhalation anesthesias —

---

[16] Althabe, O., Aranburu, G., Schwarcz, R. and Caldeyro-Barcia, R.: "Influence of the Rupture of Membranes on Compression of the Fetal Head During Labor". Scientific Publication No. 185, World Health Organization 1969.

[17] 21 C.F.R. 1.105(e)(2)(i).

none of which have been proved safe for the unborn child. There is now evidence that many of these drugs can bring about deviations or modifications in the behavior and response of newborn infants which may persist 3 to 5 days or even longer.[18] The long term implications of these deviations are unknown.

American unborn and newborn infants are routinely subjected to obstetric medications and consequent procedures that would appall midwives and obstetricians serving in such high-risk maternity facilities as the University Hospital in Amsterdam. In this teaching facility, where approximately one in every three obstetric patients is of non-Dutch descent, every effort is made to avoid pharmacologic intervention in the normal process of labor and birth. Strong emphasis is placed on preparing expectant mothers to cope with the childbearing experience. Parturient women are encouraged and strongly supported in a way that they need little or no medication. The Dutch avoidance of intervention in the normal process of parturition may well be reflected in the fact that the incidence of resuscitation (oxygenation, assisted ventilation, intubation) in this high-risk institution is approximately one in every 400 births — a record unmatched by any American hospital. In less high-risk Dutch maternity facilities 1000 births may occur without the need for resuscitation.

While European obstetricians and midwives grow concerned if the hands and feet of a newborn infant fail to "pink-up" within a minute or two after birth, in contrast, blue-tinged hands and feet at one hour, and even one day of life are so commonplace among American newborn infants that such a condition is now accepted as normal. Those who cite our air conditioned delivery rooms as the cause of the newborn's blue tinged extremities have probably never experienced the chill of a typical, lofty ceilinged European maternity facility.

---

[18] Cohen, S. and Olson, W.: "Drugs Which Depress the Newborn", Pediatric Clinics of N.A., 17:835-850, 1970.
Bowes, W., Brackbill, Y., Conway, E. and Steinschneider, A.: "The Effects of Obstetrical Medication on Fetus and Infant", Mono. Soc. Research Child. Devel. No. 137: Vol. 35, June 1970.

What is the significance of these differences in infant outcome between the United States and other developed countries? We do not know, but the statistics indicate a need to reevaluate our entire perinatal care program and in particular, our present practices regarding drugs and the childbearing woman.

According to Jerold Lucey, M.D., former Chairman of the Committee on Fetus and Newborn of the American Academy of Pediatrics: "Many of our accepted practices are not supported by scientific research and appear to be rooted more in hospital and medical tradition than in human physiology".[19]

Can we justify leaving any stone unturned when the latest available statistics indicate that:

- There are 15 developed countries whose rates of infant mortality are less than that of the United States.
- The United States now leads all developed countries in the rate of infant deaths resulting from birth injury and respiratory distress.
- The United States and Canada, whose obstetrical care is similar to our own, now leads all developed countries in the incidence of infant deaths in the first day of life.

---

[19] From Foreword to Haire, D. B.: "The Cultural Warping of Childbirth", International Childbirth Education Association News, Spring 1972.

While our incidence of infant death is a source of deep concern, it is short-sighted to evaluate a system of care only on the number of newborn infants who survive or succumb. For every newborn infant who dies of birth injury or respiratory distress there are likely to be hundreds who survive such trauma only to be damaged. Reputable United States health agencies estimate that:

1. There are 6 million retarded children and adults under the age of 65 in the United States today, with an anticipated increase of 100,000 to 200,000 this year.

2. One in every 33 children born today in the United States will eventually be diagnosed as regarded.

3. One in every 6 children shows evidence of positive or borderline minimal brain dysfunction — an estimated total of 7 1/2 million children.

4. The number of hyperactive children in the United States who require treatment or special care is growing to staggering proportions — 35,000 in the city of Los Angeles alone.

5. Three quarters of a million American children are under psychiatric treatment — a 63% increase in such children between the years 1965 and 1971. (These figures do not include the number of private patients and other children who did not visit hospitals or established mental health centers.)

While genetics, heredity and nutrition have long been recognized as affecting mental potential, it is becoming increasingly apparent that obstetrical drugs can also affect the mental development of the child and future adult.

There is no doubt that adverse socioeconomic conditions contribute to our high incidence of infant mortality and morbidity, but social pathology has become the scapegoat for those who would prefer to bury their heads in the sand like the proverbial ostrich, ignoring the fact that there are still a significant proportion of perinatal deaths and damaged children among infants who are full size, full term and from middle class homes.[20] The incidence of retarded, brain damaged or dysfunctional children cuts through every stratum of our society.

Recent evaluations suggest that transient oxygen depletion in utero and at birth may have life-long adverse effects on the developing child and future.adult. In a retrospective survey of the health histories of 1000 children with learning disabilities, cyanosis at birth, of sufficient degree to require resuscitative measures, was found to be the second most common factor ("Complicated Delivery" was first) in the health history of the children studied.[21] Such a retrospective study, while frought with inadequacies, points to the fact that we cannot afford to be complacent about the frequent need for resuscitation at birth or secondary depression so frequently seen in American newborn infants 30 to 60 minutes after a medicated birth.

In his comprehensive review of the literature, "Drugs which Depress the Newborn", Cohen cites the works of Stechler, Borgstedt and Kron and states,

---

[20] Gruenwald, P.: "Perinatal Death of Full Size and Full Term Infants", Am. J. Obstet. Gynec., 107:1022-30, 1970.

[21] Hoffman, M.S.: "Early Indications of Learning Problems", Academic Therapy, VII #1, 1971.

"These reports indicate that the behavior of infants born to mothers who receive drugs during labor is different from the behavior of infants whose mothers receive (less or) no drugs. They provide no data about long-term effects of these early drug-related behavioral differences...we remain ignorant of the possible long-term effects of drugs upon the growth and development of the child."[22]

As new techniques become available for testing the effects of obstetric drugs and procedures on the fetus and infant it becomes increasingly apparent from the evidence gained therefrom that we can no longer rely on the Apgar Score or on clinical observation alone to demonstrate the safety of a given procedure or drug. An infant may show no signs of respiratory distress and score well on the Apgar Score, while a more scientific evaluation of the infant's condition may indicate lingering signs of oxygen deprivation in utero and/or alterations in the functioning of the central nervous system.

We do not know the degree of oxygen depletion an unborn or newborn infant can tolerate before he sustains permanent brain damage or dysfunction, or death, yet drugs which are known to increase the incidence of maternal hypotension and fetal bradycardia — conditions associated with oxygen depletion in the fetus — are frequently administered to parturient women in the U.S. without their being made aware of the possible hazards or the alternative therapy.

Damage to the fetal central nervous system resulting from oxygen depletion during labor and birth may be more subtle and far-reaching than was once assumed. In a prospective study of six-year-olds who had experienced varying degrees of asphyxia at birth Ucko noted that those children who experienced asphyxia of sufficient degree to require resuscitation, although normal in manner under ordinary conditions, demonstrated significantly more behavioral disturbances when faced with a stressful situation than did the matched controls.[23]

---

[22] Cohen, S. and Olson, W.: "Drugs Which Depress the Newborn", Pediatric Clinics of N. A., 17:835-850, 1970.

New techniques for evaluating the effects of meperidine on the newborn infant indicate that as small a dosage level as 50 milligrams of meperidine can cause measurable deviations in normal newborn infant response.[24] There is no scientifically controlled research which vindicates these deviations as being without harmful sequelae. The safety of meperidine has never been established and there are now data to cause concern about its frequent obstetric use.

Research being carried out by Brackbill[25] indicates that (a) obstetrical drugs do affect infant functioning adversely and in proportion to dosage, (b) that the adverse effects of drugs are not transient, and (c) that different levels of functioning are differently affected by obstetrical drugs. Those functions most vulnerable to medication effects are also those most clearly related to later cognitive functioning.

We do not know the long term effects on the child of fundal pressure, forceps compression of the fetal head and traction on the fetal spinal column, and yet

---

[23] Ucko, L.: "A Comparative Study of Asphyxiated and Non-Asphyxiated Boys from Birth to Five Years". Develop. Med. Child. Neurol., 7:643-657, 1965.

[24] Morrison, J. et al: "Metabolites of Meperidine Related to Fetal Depression", Am. J. Obstet. Gynec., 115:1132-1137, 1973.

[25] Brackbill, Y., et al: "Obstetrical Premedication and Infant Outcome", In Press, Am. J. Obstet. Gynec., 1973.

American women are frequently administered drugs during labor which are known to increase the incidence of prolonged labor and obstetrical intervention.

Nor do we know the long term effects on the neurological and mental development of the child of chemically initiating or stimulating labor. Those who would justify the elective use of labor stimulants on the grounds that the electronic monitor will identify deviations in normal fetal physiology should be reminded of or alerted to the fact that we do not know the long term effects of electronic fetal monitoring on the development of the child, and that therefore the device should only be used when medically indicated.

Recent evidence indicates that perinatal damage resulting from drugs prescribed for or administered to pregnant, parturient or lactating women may not become evident for many years. For example, the maternal use of diethylstilbestrol, taken by obstetric patients to forestall premature labor, has been noted to contribute to, or increase, the incidence of adenocarcinoma in subsequent live-born female offspring many years later. It has been estimated that diethylstilbestrol was prescribed for approximately one million pregnant women during the period 1960 to 1970, and that between 10,000 to 15,000 young women are likely to be affected by the drug.

Nor do we know the possible long-term effect of administering diethylstilbestrol or other lactation suppressants to millions of American women immediately postpartum in order to suppress lactation, particularly since, according to a survey of midwives serving clinic patients in New York City, many of these mothers proceed to breast-feed their babies once they are home from the hospital and have more privacy.

We cannot look to the federally sponsored Collaborative Perinatal Study to guide us to a safe form of analgesic or anesthetic agent for childbearing, for the Collaborative Study did not include a sufficient control group of normal, unmedicated mothers and their babies which could have served as a base line against which to measure deviations in normal newborn infant behavior and response.

If the American public is to be protected against a false assumption of safety regarding drugs and devices used by pregnant, parturient and lactating women, the FDA must require that all manufacturers including manufacturers of pre-1963 drugs and devices submit scientific data which demonstrates the long term as well as the short term safety of their product to the unborn child. Such evaluations can be done and MUST be done. There is no reason to assume for example that, because a drug such as meperidine was on the market prior to the improved regulations issued in 1962, it is, therefore, harmless. It would seem only common sense that those drugs which are most frequently administered to pregnant, parturient and lactating women in the U.S. should be the first to be required to submit proof of safety for the child as well as the mother.

In view of the present lack of knowledge as to the effects of obstetrical medication on the long term physical, neurological and mental development of the child we strongly recommend that the FDA take the following actions:

1. The FDA should require that every manufacturer provide clinical data which indicate that his product or drug is safe as to its effect on the physical, neurological and mental development of the child before it is approved for sale or general use by childbearing women.

In view of the fact that there is no animal which duplicates human physiology, such clinical proof is essential. The FDA clearly has statutory authority in the area of approved new drugs, concerning which its statutory mandate is to set standards for testing prior to use,[26] to impose and enforce such regulations.

2. The FDA should require that all investigations carried out to establish the safety of a product include an informed control group made up of an adequate number of normal unmedicated mothers and their offspring to serve as a base line against which to measure deviations in normal newborn infant behavior and response.

3. The FDA should impose a similar requirement for proof of short and long term safety for the fetus and newborn infant on all currently used obstetrical drugs including drugs which were marketed prior to the New Drug Act of 1962.

4. The FDA should require manufacturers of both FDA sanctioned and approved drugs and devices to carry out on-going follow-up information-gathering and require recordkeeping and reports of clinical experience to the FDA in order to evaluate the long-term effects of sanctioned and approved drugs.

---

[26] Act Sec. 505, 21 U.S.C.A. Sec. 355. It should be noted that the Act specifically allows investigational use of new drugs, prior to approval, but sets strict standards for their investigational use; one such standard is that the physician obtain an informed consent from his patient, Act Sec. 505(i), 21 U.S.C.A. Sec. 355 (i). As the law now stands, it seems that a mother is probably competent to consent to procedures involving both herself and her unborn child, see, for example, the abortion cases, Roe v. Wade, 93 S.Ct. 705 (1973); Doe v. Bolton, 93 S.Ct. 739 (1973), which would imply this theory although they do not state it.

Such action is now required by statute for new drugs.[27] Expanding such requirements to all drugs would in effect be to consummate the proposal outlined in the previous paragraph, i.e. the FDA could use its power to make manufacturers of all drugs systematically acquire results of independent research and report them to the FDA.

5. The FDA should require that package insert sheets and promotional material for any drug presently on the market which has not been proven safe as to its long-term effects on the infant contain an appropriate bold type (10 point modern) warning that these effects are unknown.

6. The FDA should require the manufacturer to clearly indicate in the insert sheet, labeling, etc. that it is impossible to predict what will constitute an overdose to the fetus of a given medication or a combination of drugs, because of the infinite variations in metabolism in both mother and fetus.

With regard to the two preceding points (Nos. 5 & 6) the present FDA regulation governing package inserts reads in part as follows:

> "Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routines, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners

---

[27] Act Secs. 505(e), 505(j), 21 U.S.C.A. Secs. 355(e), 355(j).

> licensed by law to administer the drug can use the drug safely and for the purposes for which it is advertised or represented..."[28]

The FDA can simply issue an administrative interpretation of the word "precautions", stating that it requires that package insert sheets carry a warning such as the following:

> "When administered to or taken by a pregnant or childbearing woman the effect of this drug on the subsequent physical, neurological and mental development of the child is unknown. Since even the short-term direct and indirect effects of this drug vary with the individual physiology of each mother and her unborn child, the term 'overdosage' as it applies to the fetus cannot be defined for this drug."

7. The package insert sheet should also include the following additional warning, if applicable:

> "The use of this drug by childbearing women may slow the transfer of oxygen from the maternal circulation to the fetus, may prolong labor and/or may inhibit spontaneous birth, thereby increasing the likelihood that obstetrical intervention may become necessary."

If, of course, the FDA feels that an administrative interpretation of the existing rule is for some reason inappropriate, it should use its clear statutory authority over labeling[29] to promulgate a new regulation, or an amendment to the current one, stating that revelation of direct and indirect side effects must include disclosure of these possible consequent effects of the products used.

---

[28] 21 C.F.R. 1.106(b) (3) (i).

[29] Act Sec. 502, 21 U.S.C.A. Sec. 352.

8. The FDA should require the manufacturer to include in the package insert sheet and other labeling the average lapsed time between the administration of the drug to the parturient woman and the uptake of the drug by the fetal circulation and also the average time of immediate maximum impact on the fetal physiology. The FDA authority to take this step is the same as in points 5 and 6 above.

The following wording could be used:

> "The time lapse between the administration of this drug to a pregnant or parturient woman and the uptake of the drug by the fetal circulation, and the immediate maximum effect of this drug on fetal physiology is relative to the dosage given and the route and method of administration. (As indicated above, the long term effect of this drug on the development of the child is unknown.)"

Recommended Dosage	Route of Administration to Mother	Average Uptake by Fetal Circ.	Average Time of Immediate Max. Impact on Fetal Physiology
	Intravenous Inject.		
	Intramuscular Inject.		
	Intravenous Infusion		
	General Anesthesia		
	Regional Anesthesia		
	Epidural		
	Peridural		
	Saddle		
	Spinal		
	Paracervical		

9. The FDA should revoke the advertising exemption which it has granted, under which "reminder" advertising need not contain information relating to "side effects, contraindications and effectiveness." The FDA

should require that a warning or warnings similar to those suggested in Points 5 and 6 be contained in all advertising for any drug currently on the market which has not been proved safe as to its long-term effects on the child.

The FDA's statutory authority to take such a step is clear and beyond question; the Act grants the power to the FDA to require that all drug advertising contain a "brief summary relating to side effects, contraindications, and effectiveness as required in the regulations."[30] The current regulation exempts from the "brief summary" requirement

> "Reminder advertisements if they contain only the proprietary or trade name of a drug...and, optionally, information relating to dosage form, quantity of package contents, price, the name and address of the manufacturer, packer or distributor or other written, printed or graphic matter containing no representation or suggestion relating to the advertised drug..."[31]

The exemption is broad enough to vitiate effective disclosure of side effects, contraindications, and effectiveness to the physician.

10. The FDA should require that package insert sheets and labeling be systematically reviewed and updated every two years and sooner in emergencies to accord with new information. Here again the FDA clearly has statutory authority under its powers concerning labeling[32] and dissemination of information.[33] Knowledgeable consumer groups should be invited to participate in this updating process.[34]

---

(30) Act §502(n)(3), 21 U.S.C.A. §352(n)(3). In this regard it should be noted that while the Federal Trade Commission ("FTC") has jurisdiction over false advertising, 15 U.S.C.A. §45, the FDA has overlapping jurisdiction which, by agreement with the FTC, gives it primary responsibility for regulating prescription drug advertising and labeling. 36 Fed. Reg. 18, 539 (1971).

(31) 21 C.F.R. 1.105(e)(2)(i).

11. The FDA should require that physicians and pharmacists make available package insert sheets to the consumer upon request. This again can be done under the present power of the FDA to "cause to be disseminated information regarding drugs...in situations involving, in the opinion of the Secretary (FDA), imminent danger to the health or gross deception of the consumer"...[35]

12. The FDA should move to establish an official FDA pharmacologic guide.

13. The FDA should use its present powers, as it has done in the case of oral contraceptives and diethylstilbestrol[36] to require that an updated comprehensive information sheet, written in lay language and presented in 10 point modern type, which would include but not

---

[32] Act Sec. 502, 21 U.S.C.A. Sec. 352.

[33] Act Sec. 702, 21 U.S.C.A. Sec. 375

[34] In this connection we are in agreement with Dr. Henry E. Simmons, former Director of the Bureau of Drugs of the FDA, who stated that the majority of labels and package inserts "fail in their primary purpose of providing the physician, and pharmacist, with balanced authoratative and objective guides to prescribing or dispensing the drugs in question." Simmons, *supra*, 119-120.

[35] Act Sec. 705, 21 U.S.C.A. Sec. 375.

[36] 21 C.F.R. 130.45.

be limited to the warnings suggested in Points 5 and 6 above, if applicable to the drug, be provided to the obstetric patient as far in advance of the administration of obstetrical drugs as possible, in order that the patient's informed consent to the administration of the drug be obtained. The statutory authority for such action again exists under the FDA's power to disseminate information in situations endangering the public health or involving gross deception of the consumer.[37] A copy of the oral contraceptives guidelines are appended to this paper as an example of how such a warning can be achieved. It should be noted that, as described above, the potential danger to the public health from obstetrical medications may be far greater than that from oral contraceptives.

---

[37] Act Sec. 705, 21 U.S.C.A. Sec. 375.

We appreciate the fact that to carry out our proposals it will entail expensive research, but the alternative is to continue the present practice of using the general public and unborn children to establish the long term safety of a drug or device, rather than limit the investigation to a sufficient number of informed subjects and normal unmedicated controls. Our present system may well be far more costly in the long run than the cost of research which could be absorbed by the manufacturer.

The recent tragic findings of adenocarcinoma in young girls and women, whose mothers were given diethylstilbestrol in order to retain the pregnancy, is evidence that our present system is inadequate at best, and possibly the precipitator of future tragedy.

The present state of laxity is not difficult to understand. In the past, by necessity, we have had to depend on relatively crude methods and techniques to evaluate the relative safety or hazards to the unborn child of a given drug or device. The Apgar Score, which has been invaluable in bringing attention to the newborn infant, is a crude technique, by today's standards, for measuring the newborn infant's state of well-being.

We must not be misled into complacency because the methods employed yesterday or today have been unable to demonstrate adverse effects of a product sanctioned or approved for sale or use by the FDA. As more sophisticated investigatory techniques and methods become available the FDA must insist that manufacturers continue to fund research, contracted out by the FDA or National Institute of Health, in order that the safety of their product (s) be reevaluated from time to time.

INFORMED CONSENT

In this age of informed consent, the obstetric patient has the right to be made aware of the possible hazards and potential dangers to herself and to her unborn child inherent in drugs administered to her. Ideally, this information should reach the mother prior to her hospital confinement while she still has time to prepare herself to cope with the birth experience with a minimum of or no medication. Failure to provide the mother with this information in advance of her hospitalization should not, however, be used as an excuse to deprive her of this vital information before a drug is administered to her.

A competent adult patient has always had the right to decide what shall be done to his or her body and is entitled to the opportunity to consent to medical treatment. Such consent is meaningless unless a patient knows of the risks and side effects as well as the possible benefits involved in in such treatment. The doctrine has been embraced to at least some degree in most United States jurisdiction:[38]

> "Recent judicial decisions in the area of informed consent have imposed an affirmative duty of disclosure upon physicians, whether or not the patient inquires as to specific

---

[38] Alaska(*Patrick* v. *Sedwick*, 391 P. 2d 453 (1964)); Arizona (*Shetter* v. *Rochelle*, 2 Ariz. App. 358, 409 P. 2d 74 (Ct. App. 1965)); California (*Cobbs* v. *Grant*, 104 Cal. Rptr. 505, 502 P. 2d 1 (1972)); Colorado (*Mallet* v. *Pirkey*, 466 P. 2d 466 (Colo. 1970) and *Stauffer* v. *Karabin*, 492 P. 2d 862 (Ct. App. 1971)); Delaware (*DeFelippo* v. *Preston*, 53 Del. 539, 173 A. 2d 333 (1961)); District of Columbia (*Canterbury* v. *Spence*, 464 F. 2d 772 (D.C. Cir. 1972)); Florida (*Bowers* v. *Talmadge*, 159 So. 2d 888 (Ct. App. 1963); *Russell* v. *Hardwick*, 166 So. 2d 904 (Ct. App. 1964), *Ditlow* v. *Kaplan*, 181 So. 2d 226 (Ct. App. 1965), and others); Hawaii (*Nishi* v. *Hartwell*, 473 P. 2d 116 (Hawaii, 1970)); Illinois (*Green* v. *Hussey*, 127 Ill. App. 174, 262 N.E. 2d 156 (Ct. App. 1970));

> risks...(T)he number of cases in which the doctrine of informed consent has been asserted...is steadily increasing."[39]

The Commission on Malpractice of the Secretary of Health, Education and Welfare, added that it found "that there is a generally recognized right of a patient to be told about the danger inherent in proposed medical treatment."[40]

Thus, the physician is under an increasing obligation to provide detailed, accurate information. Fortunately this obligation is gaining increasing recognition

---

38 (Cont.) Iowa (Grosjean v. Spencer, 140 N.W. 2d 139 (Iowa, 1966)); Kansas (Natanson v. Kline, 186 Kan. 393, 350 P. 2d 1093 (1960), rehearing denied 187 Kan. 186, 354 P. 2d 670 (1960), Williams v. Menehan, 191 Kan. 6, 379 P. 2d 292 (1963)); Michigan (Roberts v. Young, 369 Mich. 133, 119 N.W. 2d 627 (1963)); Minnesota (Bang v. Charles T. Miller Hospital, 251 Minn. 427, 88 N.W. 2d 186 (1958)); Missouri (Mitchell v. Robinson, 334 S.W. 2d 11 (Mo. 1960) and Aiken v. Clary, 396 S.W. 2d 668 (Mo. 1965)); Montana (Collins v. Itoh, 503 P.2d 36 (Mont. 1972)); Nevada (Corn v. French, 71 Nev. 280, 284 P. 2d 173 (1955)); New Jersey (Kaplan v. Harris, 96 N.J. Supr. 242, 232 A.2d 840 (A.D. 1967)); New Mexico (Woods v. Brumlop, 71 N.M. 221, 377 P.2d 520 (1962)); New York (Fiorentino v. Wenger, 19 N.Y.2d 407, 280 N.Y.S. 2d 373, 227 N.E. 2d 296 (1968)); North Carolina (Watson v. Clutts, 262 N.C. 153, 136 S.E. 2d 617 (1964)); Oregon (Getchell v. Mansfield, 489 P. 2d 953 (Ore. 1971)); Pennsylvania (Gray v. Grunnagle, 423 Pa. 144, 223 A. 2d 663 (1966)); Rhode Island (Wilkinson v. Vesey, 295 A. 2d 676 (R.I. 1972)); South Dakota (Block v. McVay, 126 N.W. 2d 808 (S.D. 1964)); Texas (Wilson v. Scott, 412 S.W. 2d 299 (Tex. 1967)); Washington, Zebarth v. Swedish Hospital, 81 Wash. 2d 12, 499 P. 2d 1 (1972)); Wyoming (Govin v. Hunter, 374 P.2d 421(Wyo. 1962)).

[39] Department of Health, Education and Welfare, 29 (1973), Report of the Secretary's Commission on Medical Malpractice.

[40] Ibid.

in the medical profession itself.[41]

Although the law, as it has evolved thus far, has not dealt specifically with obstetrics and the treatment of pregnant women, this area is potentially one in which informed consent law may develop considerably. There are serious risks, particularly to the unborn child, which usually are not disclosed to patients, particularly in the area of administration of drugs to women during labor, birth and the immediate postpartum period. It is also an area in which many hospitals share the risks and the responsibilities of the physician, because hospital employees routinely administer the drugs.

Inadequate package inserts increase the legal vulnerability of the physician because they provide evidence of what a physician should know. Thus, it seems clearly essential to remove any "reminder" advertisement exemption and to support stricter control of the contents of package inserts and of testing, which provides information for inserts. Such regulatory actions would create for the physician an opportunity, through a uniform, coherent system, to know what a court or jury might deem him reasonably obligated to know.[42]

---

[41] The standards relating to informed consent are being upgraded by action of the medical community itself. The profession's most recent statement on informed consent is contained in the Patient's Bill of Rights, which was published by the American Hospital Association on January 8, 1973. The relevant sections of the document read as follows:

> "2. The patient has the right to obtain from his physician complete current information concerning his diagnosis, treatment, and prognosis in terms the patient can be reasonably expected to understand. When it is not medically advisable to give such information to the patient, the information should be made available to an appropriate person in his behalf...
>
> "3. The patient has the right to receive from his physician information necessary to give informed consent prior to the start of any procedure and/or treatment. Except in emergencies, such information for informed consent, should include but not necessarily be limited to the specific procedure and/or treatment, the medically significant risks involved, and the probable duration of incapacitation. Where medically significant alternatives for care or treatment exist, or when the patient requests information concerning medical alternatives, the patient has the right to such information. The patient also has the right to know the name of ther person responsible for the procedure and/or treatment.
>
> "4. The patient has the right to refuse treatment to the extent permitted by law, and to be informed of the medical consequences of his action."

More complete dissemination of drug information to the public through a patient's information sheet would provide a defense for the physician against informed consent suits. When a patient is given a brochure detailing, in language the patient can understand, the possible hazards or complications which can result from the use of a drug, the patient has the option of reading or ignoring it. She may, of course, seek further advice from her physician, but the physician would have in the first instance, fulfilled his obligation of informing her by providing her with an FDA-approved summary. The patient will no longer be deluded into thinking no risks are involved.

Health professionals who resist the concept of informed consent regarding obstetrical medication, frequently warn that mothers will be traumatized by a drug-free labor and birth. There is no research which supports this premise. Nor is there any evidence in such countries as the Netherlands or Sweden that a drug-free parturition will leave the mother traumatized by the experience.

---

[42] This situation might arise outside the context of informed consent law as well. There is some legal authority viewing package inserts and similar manufacturer summaries as evidence of what a medical professional should know in other situations. See, e.g. Monk v. Doctor's Hospital, 403 F. 2d 580 (D.C. Cir. 1967); Nolan v. Dillon, 261 Md. 516, 276 A. 2d 36 (1971); Crouch v. Most, 78 N.M. 2d 406, 432, P. 2d 250 (1967); Sanzari v. Rosenfeld, 34 N.J. 128, 167 A. 2d 625 (1961); Julien v. Barker, 75 Idaho 413, 272 P. 2d 718 (1954); Meier v. Ross General Hosp., 71 Cal. Rptr. 903, 445 P. 2d 519 (A.D. 1968); Marchese v. Monaco, 52 N.J. Super. 474, 145 A. 2d 809 (A.D. 1958); Salgo v. Leland Stanford Jr. Univ., 154 Cal. App. 2 d 560, 317 P. 2d 170 (1957).

Offering the mother accurate printed information, written in lay language, on the relative convenience and possible hazards of commonly used obstetrical medications and practices, prior to her confinement, may seem a nuisance to the practitioner, but informing the patient not only protects the hospital or professional from potential liability resulting from failure to obtain informed consent, but also permits the mother to share in the responsibility for her own well-being and that of her child.

This is also the era of increasing drug manufacturer liability for failure to provide adequate warnings about the nature and side effects of their products. The FDA will not act against drug companies which comply with its regulations and requests for supplementary information. A number of recent court decisions, however, have imposed state tort liability on drug manufacturers for injuries to patients which resulted wholly or in part from what the courts have viewed as the manufacturers' failures to disseminate adequate warnings to physicians concerning their products despite compliance with FDA standards.[43]

---

[43] Schenebeck v. Sterling Drug, Inc. 423 F. 2d 919 (8th Cir. 1970); Basko v. Sterling Drug, Inc., 416 F. 2d 417 (2nd Cir. 1969); Kershaw v. Sterling Drug, Inc., 415 F. 2d 1969 (5th Cir. 1969); Tinnerholm v. Parke, Davis & Co., 408 F. 2d 48 (2d Cir. 1969); Stromsodt v. Parke, Davis & Co., 411 F. 2d 1390, aff'ing 257 F. Supp. 991 (D.N.D. 1966); Davis v. Wyeth Laboratories, 399 F. 2d 121 (9th Cir. 1968); Yarrow v. Sterling Drug, Inc., 408 F. 2d 978 (8th Cir. 1967), aff'ing 263 F. Supp. 159 (D.S.D. 1967); Sterling Drug, Inc., v. Cornish, 370 F. 2d 82 (8th Cir. 1967); Stevens v. Parke, Davis & Co., 9 Cal. 3d _____, Cal. Rptr. 45, 507 P. 2d 661 (1973); Incolllingo v. Ewing, 444 Pa. 263, 282 A. 2d 206 (1971); Bine v. Sterling Drug, Inc., 422 S.W. 2d 603 (Mo. 1968); Krug v. Sterling Drug, Inc., 416 S.W. 2d 143 (Mo. 1967).

No court has held that a manufacturer can be held liable for failing to warn of risks of which it could not reasonably know. But at lease one court has said that the first case of a serious side-effect can be reasonably foreseeable.[44] Some courts take cognizance of the special status of prescription drugs and the physician's role in their use and thus have distinguished cases disallowing recoveries for allergic reactions for over-the-counter products, imposing a stricter standard for prescription drugs.[45]

These courts emphatically are not impressed by FDA regulatory standards; for example, the following statement is often quoted or paraphrased:

> "Although all of the Government regulations and requirements had been satisfactorily met in the production and marketing..., the standards promulgated were minimal..."[46]

In light of this still relatively small but expanding body of law, it seems to be in the interest of the drug manufacturers to support stricter FDA standards for testing and for the updating and dissemination of information to both physicians and patients. Such standards might provide a legally cognizable standard of conduct for dissemination of information which would help to insulate them against state tort law liability. The current suits against drug companies are in many ways parallel to informed consent suits, and the same policy considerations and concepts of patients' rights apply. In this regard it should be noted that if another thalidomide-type disaster occurred this time in the United States, it would subject the manufacturers to extremely high monetary damages. It is generally acknowledged that the new drug provisions were added to the Act in 1962 in order to prevent a thalidomide disaster, and it is clearly in the interests of drug manufacturers, as well as the medical profession and the public, to insure that the FDA uses all of its power, both under the amendments and the rest of the Act, to prevent such a disaster from occurring.

---

[44] Stromsodt v. Parke, Davis & Co., 257 F. Supp. 991 (D.N.D. 1966).

[45] See e.g., Sterling Drug, Inc. v. Cornish, 370 F. 2d 82 (8th Cir. 1967); Bine v. Sterling Drug, Inc., 422 S.W. 2d 603 (Mo. 1968); Krug v. Sterling Drug, Inc. 416 S.W. 2d 143 (Mo. 1967). One case extended this warning requirement to the general public when a prescription polio vaccine was dispensed at mass clinics, Davis v. Wyeth Laboratories, Inc., 399 F. 2d 121 (9th Cir. 1968).

[46] Stromsodt v. Parke, Davis & Co., 257 F. Supp. 991, 997 (D.N.D. 1966).

Mr. GORE. Thank you very much. I hope you are pleasantly surprised at the reaction of FDA to this hearing and subsequent proceedings. I would direct the attention of the FDA to the statement of the ranking minority member which appears in the record of this proceeding at the outset. There is a bipartisan concern and it is a matter that has festered for far too long and even those who may take exception to some of the statements in your testimony must concede that even from their point of view there is a great deal of it that is right in the center of the bulls eye and it must be responded to.

Before we go to questions I have the pleasure of calling upon our colleague from New York, Jonathan Bingham. It has been my experience as a new chairman of this subcommittee exploring issues of concern to the public that there have been many who have preceded Mr. Shamansky and me in these areas and one such pioneer in this area is Jonathan Bingham who has introduced legislation long since. We will put the entire text of your statement in the record and invite you to proceed with any or all of it as you see fit. Welcome.

STATEMENT OF JONATHAN BINGHAM, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

Mr. BINGHAM. Thank you very much, Mr. Chairman and members of the committee. It is a pleasure to appear before you and I appreciate the opportunity of doing so. I am particularly glad to be able to do so along with Mrs. Haire to whom we owe a very distinct debt of gratitude for helping in the formulation of the legislation that I have introduced both in this session of Congress and in the past Congress.

I have been interested in this subject for a long time and I certainly want to salute you Mr. Chairman, for having these hearings. I think it is a topic of enormous importance and one that has not been paid sufficient attention. It was first brought to my attention by a constituent of mine by the name of Estelle Cohen who had the experience of having a child born in the course of artificially stimulated labor and that child has suffered brain damage at the time and it has, the event has caused Mrs. Cohen to make kind of a life work of trying to stimulate governmental action in this field to see to it that such procedures are not routinely followed, the dangers are recognized and that many of the actions that Mrs. Haire has spoken of are taken. I have appended to my testimony an article from the Co-op City News which is published in my congressional district describing Mrs. Cohen's experience in detail. I hope that may be added to your record.

Mr. GORE. Without objection we will put that in and the text of your bill, H.R. 138 into the record of this proceeding at the end of your statement.

Mr. BINGHAM. I realize and I am sorry that it is a fact that that bill has been referred to other committees in view of your interest I wish it had been referred to this committee.

Mr. GORE. I serve on the Energy and Commerce Committee also so we will be watching for it over there.

Mr. BINGHAM. I hope you will be able to pursue it there. Let me just mention some of the main provisions of the bill. It would under the Social Security Act require States to provide women access to their obstetric medical records and current information on obstetrical procedures. For example any health care practitioner or provider of services to a woman during pregnancy would be required to inform the woman:

> Before performing the procedure or administering the drug or device of the side effect risks, contraindications and effectiveness with respect to the health of the woman and of her prospective children of the procedure of not performing the procedure or administering the drug or device and of performing other medically recognized procedures.

In other words alternatives instead of the procedure, drug or device involved. And after being so informed would be "required to receive the consent of the patient to the performance of the procedure." That is the first section. The second section would amend the Federal Food and Drug and Cosmetic Act by requiring the dissemination of information on the effects and risks of drugs and devices on the health of women who are pregnant and in labor and of prospective and developing children. Again to quote from the bill, explanation would have to meet guidelines established by the Secretary would have to include an explanation of:

> The side effects, risks, contraindications and effectiveness of the drug or device on the health of women during pregnancy and parturation and on the health of prospective and developing children.

The remaining section would call for a study by the Secretary of Health and Human Services on the delayed long-term effect on child development of obstetrical drugs and procedures administered to or used by women who are pregnant or in labor. Let me quote from the bill again:

> The study would need to determine long-term side effects, risks, contraindications and effectiveness of the use of obstetrical drugs, devices and procedures with respect to maternal health and child development including child development through the age of seven years. The study shall be developed and carried out in consultation with behavioral psychologists, pediatric neurologists, obstetricians and other appropriate professionals and knowledge and consumer representatives whose expertise would enhance the conduct of the study.

Again I want to say that we owe a great debt of gratitude to Mrs. Haire for the development of this legislation and I hope that with these hearings of yours calling attention to the dangers here—and

I am not going to go into that in further detail at this time because I know that Mrs. Haire has covered that and probably other witnesses will—I hope that this committee will be able to encourage the passage of legislation not necessarily my bill but something along these lines. Thank you very much, Mr. Chairman.

[The prepared statement of Representative Jonathan Bingham follows:]

TESTIMONY OF
HONORABLE JONATHAN BINGHAM
before the
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
of the
HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY
JULY 30, 1981

Mr. Chairman, Members of the Subcommittee: Thank you for the opportunity to appear before you today.

The effect of prescription drugs on the fetus during pregnancy and labor is something I have been concerned about for some time. The possible ill effects of these drugs was first brought to my attention by a constituent of mine named Estelle Cohen. Thirty years ago this month Mrs. Cohen's son Ben was born early because she was given an injection of the hormone drug, Pitocin, which artificially starts labor. Labor-stimulating drugs such as Pitocin may cause brain damage in infants by sparking longer and more frequent uterine contractions, thus decreasing the ability of the fetus to restore its supply of needed oxygen. If the fetus is deprived of oxygen long enough, brain damage can result. Severe contractions may also result in brain damage to the infant by causing cerebral hemorrhage in the fetus. Mrs. Cohen had not sought this early birth. Ben was born with brain damage, and Mrs. Cohen is reminded every day of the hazardous effects of the use of Pitocin.

With your permission, I am submitting for the record a copy of an article which appeared in the Sept. 14, 1978 issue of the Co-Op City News, published in my Congressional district, about Mrs. Cohen's experience. I hope each of you will read this tragic and moving story. One cannot help but wonder how many other Ben's there are.

In response to Mrs. Cohen's experience, and working with her and Mrs. Doris Haire, who will testify here today, I introduced "The Obstetric Care Information Act" in the last Congress. I introduced it again in this Congress and to date have 34 cosponsors.

This bill is an outgrowth of a New York State law, originally sponsored by New York State Senator Abraham Bernstein, which requires that physicians or nurse-midwives warn expectant mothers of possible harmful effects of obstetric drugs on the mothers and their babies.

My bill would do three things:

1. it would require States to provide women access to their obstetric medical records and current information on obstetrical procedures;
2. it would require the dissemination of information on the effects and risks of drugs and devices on the health of women who are pregnant or in labor and of prospective and developing children; and
3. it would provide for a study on the delayed long-term effect on child development of obstetrical drugs and procedures administered to or used by women who are pregnant or in labor.

I believe that passage of this bill would help to insure that women would be able to make more informed decisions about the use of drugs and procedures during pregnancy and delivery, and could help prevent injury to untold numbers of infants.

Our experience with the adverse effects of obstetric-related drugs, which often do not become apparent until long after the drugs have been administered to the mothers, has made us more sensitive to the need for legislation which would help prevent these tragic occurrences.

The pitiful and devastating effects of the use by mothers of the drug diethylstilbestrol - otherwise known as DES - on their offspring are well known. I have just mentioned the possible effect of Pitocin. These are just two examples of the kinds of potentially harmful effects the careless, uninformed, or misinformed use of drugs may have.

The fact of the matter is that health professionals have all too little information on the hazards or potential hazards of the use of obstetric drugs and procedures.

I call your attention to a report issued by the General Accounting Office on Sept. 24, 1979, entitled "Evaluating Benefits and Risks of Obstetric Practices - More Coordinated Federal and Private Efforts are Needed". This report confirms that, with few exceptions, drugs and procedures employed in obstetric care have never been properly evaluated and found to be in the best interest of mothers and their babies.

According to the U.S. Department of Education there are over four million children and youth in this country who are afflicted with significant mental and neurologic dysfunction. If four million children had cancer there would be an uproar, but for some reason there seems to be the general attitude that nothing can be done to prevent mental or neurological damage, and little attention is focused on it.

It is time to change that. Surely we do not have to sit back and let the numbers increase. Surely we should be more aggressive in our pursuit of answers to many pressing questions concerning drugs and their effects on the fetus.

There is so much information that needs to be developed and so many questions that need to be answered. The future of our newborn may be inadvertently altered for the worse in ways we have not yet begun to comprehend. We must begin to take a systematic look at this area.

I commend the Subcommittee for holding this hearing, and I urge you to hold further hearings and cover more ground so that the effects of both drugs and procedures can be investigated. There are so many areas that need to be explored. For example, there is an increasing use of caesarean section. Why? Does anyone really know what are the long-term effects of routine electronic fetal monitoring? And what are the effects of the use of medication to relieve labor pain? The list of questions could go on at length.

Today this Subcommittee will hear from people who are experts in areas including obstetric practices, pharmacology and bioethics. I hope you will carefully consider what you hear. Doris Haire, who has been trying for years to call attention to the need for public discussion of these matters, has a message of paramount importance.

With your permission I would like to submit for the record a copy of my bill, along with its cosponsors, and a brief list of sources of further information on the subject of this hearing.

Again, thank you for the opportunity to appear before you today. Simply by holding this hearing you have made a significant contribution to understanding a complex and vitally important area. But I hope it is only a beginning, for there is so much more that needs to be done.

To accompany the testimony of Cong. Jonathan Bingham, July 30, 1981.

Co-Op City News, Sept. 14, 1978.

RESIDENT WINS DRUG REFORM

(By Patrick McDonnell)

On July 12, 1951, a proud Estelle Cohen left Columbia Presbyterian Hospital with a "beautiful" and seemingly healthy baby boy, born several weeks before her due date.

The child, Ben, was born early because Mrs. Cohen was given an injection of the hormone drug Pitocin, which artificially starts labor.

Mrs. Cohen hadn't sought the early birth, but the obstetrician had insisted. "And I figured the doctor knew best," the Co-op City resident explains.

Today, 27 years later, Mrs. Cohen thinks differently.

Her son, Ben, was born with brain damage which Mrs. Cohen believes was brought on by the injection of the labor-inducing Pitocin (oxytocin)—commonly called "Pit."

LONELY CRUSADE

Mrs. Cohen's life has since been dominated by her son's inability to lead a normal life, and she and a few others have waged a lonely crusade to inform the public about the dangers of Pitocin and other drugs given to pregnant women by physicians.

Finally, on Sept. 1, largely through Mrs. Cohen's efforts, a new law became effective in New York State, requiring that physicians or nurse-midwives warn expectant mothers of possible harmful effects of obstetric drugs on the mothers and their babies.

The bill was ceremoniously signed into law by Gov. Carey last Tuesday, at a meeting in New York attended by Mrs. Cohen and Bronx State Sen. Abraham Bernstein, the bill's sponsor. Mrs. Cohen had first informed Sen. Bernstein three years of the potential harm of obstetric drugs.

AMERICAN HEROINE

Doris Haire, president of the American Foundation for Maternal and Child Health and an outspoken critic of many current obstetrical practices, called Mrs. Cohen "one of America's heroines," and said the new bill would "dramatically" alter the way pregnant women were treated by doctors.

Because New York is a major center for medical education, Mrs. Haire said in an interview, the "ripple effect" of the new law may soon be felt throughout the United States and abroad.

Mrs. Haire noted that the new regulation also requires that physicians inform expectant mothers that the delayed, long-term effects of certain drugs on human development are unknown.

Labor-stimulating drugs such as Pitocin may cause brain damage in infants by sparking stronger, longer and more frequent uterine contractions, thus decreasing the ability of the fetus to restore its supply of needed oxygen. If the fetus is deprived of oxygen long enough, brain damage can result.

The severe contractions may also result in brain damage to the infant by causing cerebral hemorrhaging in the fetus.

Mrs. Haire and her group also note that the strong contractions often present during induced labor make it more likely that mothers will need pain-killing drugs—which can further harm infants, depressing their respiratory ability.

NO EXACT STATISTICS

Although no precise figures are available documenting how widely labor-inducing drugs are used, it was estimated in 1975 that labor in one of ten births in the United States is induced—or actually started—by drugs, usually Pitocin. In addition, it was estimated that in one fifth of all births, labor is stimulated—or speeded up—by drugs, and Pitocin is the most widely used labor stimulant.

Mrs. Haire and her group concede that at times there are clear medical reasons for the use of labor-inducing drugs, such as when the mother has diabetes or toxemia or other conditions that may result in the death of the fetus if the pregnancy is continued.

Regarding labor-stimulation, Mrs. Haire and Mrs. Cohen point to warnings by many experts that labor should be stimulated only when uterine contractions are too weak or infrequent to result in the normal progression of the fetus through the birth canal. Ironically, one factor that may hamper the fetus' progression is the presence of pain-relieving medication in the mother.

EXPERT SPEAKS

Dr. Caldeyro-Barcia, president of the International Federation of Gynecologists and Obstetricians, has said that if labor were induced and stimulated only when it was absolutely necessary, these practices would be used in only about three percent of all U.S. births—instead of the estimated 28 percent of the births that may now involve elective induction and drugs-stimulated labor.

These procedures are used so often, Dr. Caldyro-Barcia was quoted as saying on April 9, 1975, "Because the doctor wants to finish earlier so he can do something else, or because he wants to go away for the weekend—all at the expense of the fetus."

An editorial in the prestigious British medical journal, The Lancet, on Nov. 16, 1974, stated: ". . . Induction on the grounds of social convenience is a pernicious practice which has no place in modern obstetric care. The mother's holiday, the calls of the obstetrician's private practice, must not influence, for the sake of even a few days, an event which for the child may affect the outcome of its entire life."

In a recent interview with the News, Mrs. Cohen, who works for obstetrical reform with an almost religious fervor, recalled the birth of her abnormal son, Ben, and the subsequent events that resulted in her current obsession with the issue.

ROUTINE VISIT

On July 10, 1951, she says, she went for a "routine visit" to her obstetrician at Columbia Presbyterian Medical Center. It was still several weeks before she was due to give birth.

The doctor, to whom she had been referred by her regular obstetrician, who was on vacation, informed her that she should return in two days and have labor "induced."

"I didn't even know what induction meant at that point," says Mrs. Cohen, a round-faced, brown-eyed woman who is now 57.

"I wasn't in any hurry to have the baby. I wasn't impatient . . . Some women, they feel very uncomfortable at that stage of pregnancy and they want their labor to be started artificially. I don't mind waiting until my time came . . . There wasn't a single sign of imminent labor."

Mrs. Cohen already had one son—who is now a 29-year-old department store executive—and that birth had gone smoothly.

SHE WAS UPSET

When Mrs. Cohen went home after conferring with the obstetrician, she says she was "upset and frightened."

"I had a feeling there was something wrong that the doctor wasn't telling me," she explained.

Years later, Mrs. Cohen says, she discovered what the doctor was allegedly holding back from her: That he was a research obstetrician and he was then experimenting with a new method of administering the labor-inducing drug Pitocin.

On the afternoon of July 10, Mrs. Cohen says, her husband Irving, an auditor, called the obstetrician.

"The doctor said I might have the baby on the street. He asked my husband if he wanted his wife to have her baby on the street? . . . He told my husband not to interfere."

MAKES DECISION

Mrs. Cohen then made the decision that has haunted her the rest of her life: She agreed to have labor induced, as the doctor had ordered.

"In my day," she recalls, "the doctor's word was law. The women of my generation never questioned a doctor's motives. It was taken for granted that what the doctor advised must be the right thing . . . We were wrong."

On July 12, 1951, Mrs. Cohen says she entered Columbia Presbyterian and she was given the Pitocin intravenously by an assistant. Her obstetrician, she was informed, was busy with another patient.

For a long time after the injection, she says, there were only faint contractions. "But suddenly I had a contraction so painful and sustained—it was completely different from my first birth. I expected pain, but not that . . . I was convinced that I'd never leave that hospital alive."

LEAVES HOSPITAL

But her beautiful baby Ben was born, weighing a healthy six pounds ten ounces. Five day later, Mrs. Cohen left Columbia Presbyterian with her "seemingly beautiful" child.

Before Ben was one year old, however, she began to notice that something was wrong with him.

"It was during that time after the war when everybody was having babies," says Mrs. Cohen, who then lived in Washington Heights.

"We'd all meet in the park, and Ben was different from all the other children. There were one or two retarded kids . . . But there weren't any other children like Ben."

Doctors told Mrs. Cohen they were baffled by Ben's problem, and they could find no physiological damage.

As Ben grew older, he had difficulties relating to other children.

RAN OTHER WAY

"Every day, there must have been 75 kids playing on 170th Street near our house," Mrs. Cohen recalls. "But Ben just couldn't seem to understand how to play. To the other children, and to my older son, it was easy to learn that when you hit the ball you were supposed to run to first base. But when Ben hit the ball, he'd run the other way."

FILMED FROM
BEST COPY AVAILABLE

School was another obstacle for Ben.

"He didn't want to go to kindergarten. I had to drag him out of bed every morning and dress him from scratch. At first, I even had to carry him there. It looked awful, a mother carrying a great big kid to school."

Ben spent his entire first week of kindergarten "spread-eagled on the floor," refusing to participate, says Mrs. Cohen.

BUTT OF JOKES

In elementary school in Washington Heights, she says, "he was the butt of the jokes of every tease in the class." His adjustment problems were exacerbated by his hyperactivity and by his occasional violent temper tantrums—sometimes aimed at his parents and other times at his classmates.

As doctors still insisted there was no physiological damage, Mrs. Cohen began to blame herself for her son's ailments.

"Every day I used to ask myself, 'What did I do to this poor boy to bring this on?' I felt very guilty."

Years later, Mrs. Cohen's guilt was replaced by rage when she obtained a copy of an official Columbia Presbyterian Medical Center report, dated Dec. 8, 1958, which concluded that her then four-year-old son may have sustained damage to his central nervous system—although the mother was never informed of this fact.

HE'S UNPREDICTABLE

Ironically, Mrs. Cohen thinks it may have been easier for her if Ben were born completely retarded. "Life would have been more predictable if he were retarded. As it was, the only thing that was predictable about Ben was that he was unpredictable."

Such unpredictability was illustrated by his frequent, sudden outbursts of temper, as well as by the occasional good marks he received in school, especially in science courses.

Finally, when Ben was 9, it was diagnosed that he had suffered brain damage, probably at birth. Ben's particular ailment warps his sense of time and space, as well as making it difficult for him to grasp concepts and think abstractly.

LEARNING DISABILITY

Ben's problem, which used to be referred to as "minimal brain dysfunction," is nowadays grouped under the catch-all phrase of "learning disability." Some 10 million children in the United States are thought to be suffering learning disabilities to some extent, many of them more subtle than Ben's.

Although there is little definitive proof, Mrs. Cohen and others contend that expectant mothers' increasing reliance on drugs has contributed to the postwar explosion of children with learning disabilities.

The learning problems are generally thought to be brought on by brain dysfunction, which experts believe can be caused by, among other factors, poor diet, unjury or illness of the mother during pregnancy, and inadequate oxygen during birth—which can be an effect of unnecessarily-used obstetric drugs.

Consequently, Mrs. Cohen believes her crusade against the liberal use of obstetrical drugs has ramifications far beyond her own personal cause.

"We're part of an enormous problem," she says. "We don't even know how many kids are walking around with damaged brains brought on by these drugs . . . It's easy to see the problem in my Ben, but how many other kids are going around with much more subtle damage because of the drugs? What right have we to reduce someone's intelligence by even one iota by using these drugs?"

OTHER HARMFUL DRUGS

Besides the damage done by medications given to mothers during childbirth, Mrs. Cohen notes that abnormalities have resulted in children when expectant mothers took other drugs, such as Diethystilbestrol (DES), which was prescribed to prevent miscarriages and Thalidomide, a tranquilizer.

In addition, Mrs. Cohen says, the accepted obstetrical practice in the United States of keeping women lying on their backs during labor and delivery has been criticized by many experts, who maintain that lying on one's side, sitting or squatting during childbirth is healthier for both the mother and the fetus.

But before Mrs. Cohen ever became aware of these larger issues, her son attended several different schools, until his inability to adjust persuaded her to withdraw him from George Washington High School while he was in tenth grade.

Three years earlier, in 1966, Mrs. Cohen read a magazine article entitled "Babies by Appointment?" which first led her to suspect that she had been a "guinea pig" for a research obstetrician.

ALWAYS CONTROVERSIAL

The article stated that Pitocin, the drug Mrs. Cohen had been given to induce labor, had always been controversial—not "absolutely safe and routine," as she says the doctor assured her. The article further explained how the prolonged contractions brought on by Pitocin may "clamp down on the blood vessels of the placenta, thus depriving the fetus of oxygen-carrying blood for longer periods than with a slower labor."

Mrs. Cohen was outraged.

In testimony presented last year to the Obstetrics and Gynecology Committee of the Food and Drug Administration, Mrs. Cohen related her reaction to this new found information: "I began to ask many questions. I began to suspect that a frightening situation existed in obstetrics, that people who were supposed to be protecting the welfare of our children were not aware of what was developing in our school population.

MALPRACTICE SUIT

In 1969, Mrs. Cohen started the process of filing a malpractice suit against Columbia Presbyterian Medical Center and the obstetrician who delivered her son.

In October, 1975, a jury in Manhattan State Supreme Court ruled that there was no malpractice.

Shortly before that verdict, Mrs. Cohen says, she and her husband turned down an offer from hospital attorneys to settle for $100,000 in damages.

Mrs. Cohen rejected the cash settlement, she says, because she was "absolutely convinced" of the suit's justice, and had she accepted the money she probably would have been obligated to remain silent about her complaint.

"I think that would have choked me," Mrs. Cohen says.

SHE'S ENCOURAGED

Despite her frustrating experiences, Mrs. Cohen was cheered by her successful effort to have the obstetrical-warning bill passed—even though she warns that the new law "is only a start."

She says she would like to see the movement culminate in a realization on the part of all parents that, "The protector of the child are its mother and father—not the medical profession."

FILMED FROM
BEST COPY AVAILABLE

Sources of further information on the subject of obstetric drugs and procedures, to accompany the testimony of Cong. Jonathan Bingham, July 30, 1981.

"Obstetrical Practices in the United States, 1978"; hearings before the Subcommittee on Health and Scientific Research of the Committee on Human Resources, United States Senate, April 17, 1978.

"Evaluating Benefits and Risks of Obstetric Practices - More Coordinated Federal and Private Efforts Needed"; General Accounting Office, HRD-79-85, September 24, 1979.

"A Review of Research Literature and Federal Involvement Relating to Selected Obstetric Practices"; General Accounting Office, HRD-79-85A, September 24, 1979.

"Better Management and More Resources Needed to Strengthen Federal Efforts to Improve Pregnancy Outcome"; General Accounting Office, HRD-80-24, January 21, 1980.

"Costs and Benefits of Electronic Fetal Monitoring: A Review of the Literature"; National Center for Health Services Research, U.S. Department of Health, Education and Welfare, Public Health Service.

"An Evaluation of Caesarean Section in the United States"; U.S. Department of Health, Education and Welfare, June 1979.

Mr. GORE. Thank you very much and thanks for your work in this area. I look forward to working with you. I was just talking with Mr. Grumbly, my staff director, about working with your staff on this legislation. Perhaps we can make some progress with it at the Energy and Commerce Committee and I look forward to working with you.

Mr. BINGHAM. Thank you very much.

Mr. GORE. Mr. Shamansky.

I know you have another hearing going on so I would suggest if you have questions for Congressman Bingham that we take those first.

Mr. SHAMANSKY. Congressman Bingham, have you had any response yet from the FDA or the pharmaceutical industry or organized medicine with respect to your goals?

Mr. BINGHAM. Not any significant response.

Mr. SHAMANSKY. You have just not heard from them.

Mr. BINGHAM. That is right.

Mr. SHAMANSKY. Based on your previous experience do you have any expectation of hearing from them?

Mr. BINGHAM. No. I think both the industry and the professionals in this field and the Government agencies need the kind of stimulation that this hearing should provide. I do not think they have paid enough attention to this problem.

Mr. SHAMANSKY. Do you consider this to be just a matter of neglect?

Mr. BINGHAM. Perhaps Mrs. Haire would know better than I what the motivation is. Whether it is their concern with other problems. It just has been difficult to get them to focus on this problem.

Mr. SHAMANSKY. Have you asked FDA directly yourself?

Mr. BINGHAM. Yes, we have.

Mr. SHAMANSKY. How would you characterize the response?

Mr. BINGHAM. We have not really had any satisfactory answer from them.

Mr. **Shamansky**. Thank you, Mr. Bingham.

Mr. **Gore**. Thank you very much. Mrs. Haire I see on your list of drugs commonly used in obstetrics on page three Scopalamine. Is that still used?

Ms. **Haire**. Obstetricians will usually tell you that the drug is no longer used, but nurses tell me, definitely, that it is being used. It is something I think most hospitals are ashamed of, but, nevertheless, Scopalamine is being used.

Mr. **Gore**. When my wife and I attended to the birth of our first child we went through the American Society of Psychoprophylaxis and Obstetrics, or La Maze classes, and the effects of that medication were described as being the woman continues to experience the pain but her memory of it is obliterated afterwards. She is so completely disoriented and so forth she cannot recall the pain. Is that a fair description of the bizarre effect of that drug?

Ms. **Haire**. That is the "desirable" effect.

Mr. **Gore**. That is what they want to happen.

Ms. **Haire**. I think it is tragic that many women miss the most ego-building experience a woman could possibly have. The sad thing is that many women must be treated by a psychotherapist after being administered Scopalamine during childbirth—because the drug tends to cause nightmarish effects when the mother reflects on her obstetric experience. For some women there is just enough recall to produce psychological problems. There are now psychotherapists in New York who deal only with women who been traumatized by their childbirth experience.

Mr. **Gore**. When did you first begin to work with FDA on these issues?

Ms. **Haire**. In 1969. Each year I have become more organized in my efforts. In 1973 we hired a law firm, whose particular expertise is the deciphering of Federal regulations, to examine those Federal regulations which govern the FDA. We learned from the brief they prepared for us that the vast majority of the recommendations we proposed to improve the FDA's evaluation and regulation of obstertric-related drugs could be accomplished by the FDA without any additional legislation. That brief was the baisis for my first formal presentation to the FDA in 1973.

Mr. **Gore**. 1969.

Ms. **Haire**. 1973. However, there was communication before that time.

Mr. **Gore**. Let me recognize my colleague again, Mr. Shamansky.

Mr. **Shamansky**. It is very difficult for me to address you as Mrs. Haire, so I will just say Doris. After 34 years that is the way it is going to be today. Doris, on page 6 of your testimony you criticize physicians for continuing to prescribe drugs without advising them that the drugs have not been subjected to what you consider to be proper studies. In your view what are the reasons for the physicians' reluctance, and do you consider any of these reasons to be valid?

Ms. **Haire**. The Women's Health Movement feels that some of this is due to the paternal feelings of some male physicians who genuinely care for women. Many say they do not want to bother women with all the unpleasant possibilities. But one of the obstetricians who has guided me greatly said:

> You can never get obstetricians to admit that the drugs we have been giving pregnant women are harmful, because all of us know that we have given drugs that have subsequently damaged mothers and babies. The possibility of a lawsuit is always there.

I would love to call a moratorium and say, "All of you obstetricians out there who are feeling badly about what you have done, we forgive you. Let's start over again." Obstetricians who did not know yesterday that the drugs they were giving were potentially harmful to the fetal brain cannot say that tomorrow. I hope there is broad media coverage of this hearing so the information discussed will become public knowledge.

Mr. **Shamansky**. Since you did mention that, what is the product liability experience and do we have a record of it? The lawyer in me makes me ask what about medical malpractice suits here.

Ms. **Haire**. Only the most horrendous cases ever get to court.

Mr. **Shamansky**. Is it the thrust of your approach here that you realize that there may be some risk inherent in any drug for some patients, but that you are seeking information so that there will be informed consent?

Ms. **Haire**. The woman has a right to know the risks to herself and to her baby inherent in the use of obstetric drugs. One of the risks is the uncertainty about the drug's long-term effects on the neurological development of her child. A woman has a right to know that. The physician has an obligation to so inform her. I cannot see why companies are so reluctant to provide pregnant women with information regarding the risks inherent in the use of obstetric drugs. An honest discussion of the risks would protect the manufacturer of the drug, the doctor, the hospital, and, certainly, the mother.

Mr. **Shamansky**. Let me proceed in this idea of quantification. Are there any circumstances in your mind that would make it reasonable and proper for a physician not to inform a patient of something if the degree of risk is so remote as not to be mathematically significant or do you ever agree there is such a circumstance?

Ms. **Haire**. I happen to feel all of the possibilities should be discussed.

Mr. **Shamansky**. Do you think the person who is receiving the information is qualified to respond to it because he or she is a layperson?

Ms. **Haire**. Lasagna carried out a study in which, asked a large group of laypeople if they would want to know if there were an indication of a serious adverse effect in 1 out of every 100,000 cases. The vast majority of those people said "yes." If there were an indication of a serious adverse effect in 1 out of every 50,000 cases—maybe even 100,000—I would want to know. I probably would take the drug because those are pretty good odds. However, to give my informed consent I would need to know the odds.

Mr. **Shamansky**. Did that study follow up and say what the response to that information was? In other words, you told the person 1 in 100,000. What was the response? I will take it or not take it.

Ms. **Haire**. That was not in the study. I do not think we are going to stop taking drugs because we know there are unanswered questions about the latent effects of drugs.

Mr. **Shamansky**. Doris, you made a statement on page 23 to the effect that 1 out of 10 children has some kind of impairment. Are you convinced that a high proportion or a low proportion is the result of administering drugs during pregnancy or during the delivery?

Ms. **Haire**. I cannot give you specific quantity. I feel a significant proportion of these children are the result of obstetric medication given, with the best of intentions to women during labor. Whether the drug, in itself, does the harm or whether it works synergistically with other obstetric stresses would have to be evaluated, but there is no doubt in my mind that a large proportion of the learning disabled and brain-injured children in the United States are the result of obstetric drugs.

Mr. **Gore**. The best statistical evidence we have been able to gather in preparation for the hearing indicates an enormous amount of uncertainty on this question. The low ends of the range of estimates is that 3 to 5 percent of the birth defects are caused by drugs but 75 percent of the birth defects have unknown causes, so you have a range beginning with 3 to 5 percent and possibly extending a long distance into the 75 percentile. There are disputes about how much of that 75 percentile might be related to this category. Thank you for yielding.

Mr. **Shamansky**. I would like to pursue this question of the laissez-faire attitude which you characterize the FDA as exhibiting with respect to powerful narcotics like analgesics, Nubain and Stadol as safe for use in obstetrics without first presenting evidence of safety to FDA's Fertility and Maternal Health Drugs Advisory Committee. Is this committee merely selectively used? Is it consistently used? Are there guidelines for using it and why would it not be referred to?

Ms. **Haire**. Those questions, I think, should be addressed to Commissioner Hayes because I have asked them of various FDA officials and have not been given a satisfactory answer. First, we have asked that a Perinatal Drug Advisory Committee be established. We have asked this repeatedly because none of the FDA advisory committees has the appropriate interdisciplinary makeup to properly evaluate the effects of obstetric drugs on the offspring. The Fertility and Maternal Health Drug Advisory Committee is made up essentially of obstetricians. There is a statistician and a pediatrician who comes intermittently, but you cannot expect obstetricians to have a completely unbiased view about the drugs that they have been administering to women for years. The same is true of the Anesthetic and Life Support Committee which is comprised at anesthesiologists and anesthetists. I do not think they can be expected to be completely objective about the risks of epidural anesthesia.

Mr. **Shamansky**. The lawyer in me keeps popping out. With respect to the standards for establishing a committee setting for the criteria by which it will be used, are you saying that there is simply no explanation of when this committee is used or not used? It is just however it happens to happen?

Ms. **Haire**. No explanation was given to me by the FDA.

Mr. **Shamansky**. But you did inquire?

Ms. **Haire**. Yes, I did inquire.

Mr. **Shamansky**. With John at your right hand there I am sure that that base would have been touched. But again I am responding to the idea that either you use something with consistency or you do not, but as far as you can see that information is not available.

Ms. **Haire**. A few days ago I called the FDA, because there are officers of FDA that I have found to be extremely cooperative. I asked this particular FDA officer when the drug Nubain was approved. I could not get any information. I was told the only way I would get information of that sort was through the Freedom of Information Act. I said I rather dislike having to use the Freedom of Information Act because it makes me feel as if the FDA and I are on opposite sides of the issue. Again I have tried to work with the FDA. What I was asking was if the type of limited information that was obtained for Stadol was the same type of information that they obtained on the drug Nubain.

Mr. **Shamansky**. Whatever it is, it is basically an ad hoc sort of thing. You either get cooperation from somebody but not cooperation from somebody else.

Ms. **Haire**. Right.

Mr. **Shamansky**. You could not rely on a systematic response according to standard policy available to everybody.

Ms. **Haire**. Right.

Mr. **Shamansky**. Would you be kind enough to refer to page 17 of your prepared testimony. I need some help with respect to the second incident. What basically is the problem there? I find that I am confused.

Ms. **Haire**. Regarding FDA officers?

Mr. **Shamansky**. Yes. You had three recent events. The second——

Ms. **Haire**. First, there are a great many drugs used in obstetrics which have never been approved by the FDA for that use. Of all the people in the FDA I can get the straightest answers from Dr. Martha Freeman. I asked Dr. Freeman what constitutes an FDA approved drug. She told me that only those uses mentioned in the "Indications" section of the drug's package insert were approved uses of drug.

Mr. **Gore**. The significance of that is that there are other sections of the label which imply that it has been looked at for use in pregnancy and been approved for that purpose, but that implication is completely misleading if it does not appear in the specific part of the label with the heading "Indications."

Ms. **Haire**. That is correct. My husband's eagerness to answer the question is because, in preparation for this hearing, he read the package inserts of about 55 obstetric-related drugs. So he is very familiar with the language in the package inserts. The usual answer most health professionals give is, if the package insert discusses the use of the drug in pregnancy or obstetrics then that is an indication that the drug has been approved by FDA for such use. In fact, one of the FDA officers I talked with told me that I would not find mention of the drug's use in obstetrics in a package insert without also finding that use mentioned in the Indications section. That is absolutely wrong.

Mr. **Gore**. Ms. Haire, did you want to add something to that?

Ms. HAIRE. No.

Mr. SHAMANSKY. You say that there is no list of drugs approved by the FDA as safe for use in pregnancy and obstetrics and there is no system for retrieving such information from its records?

Ms. HAIRE. That is what I was told by the Consumer Safety Officer who answered the inquiry I had addressed to Dr. Crout, Director of the Bureau of Drugs.

Mr. SHAMANSKY. Have you had any responses or have you made any inquiries of the medical schools? I know you are a friend and admirer of Dr. Emanuel Friedman of Harvard Medical School and you have contact with people like that. What is the response of those physicians, who I am assuming would be—shall we say—more free of whatever considerations that the average obstetrician or pediatrician might feel he or she was subjected to.

Ms. HAIRE. Again I think you have the same pressures on all obstetricians, not to discuss the relative risks with their patients, particularly physicians who work in medical schools. There is no doubt in my mind that in many cases drugs are given to women by individuals in training in cases where, with a little effort, the use of the drug could have been avoided.

Mr. GORE. I find it absolutely incredible that they do not have any system for retrieving that information. We have checked and that apparently is the case. It would seem to indicate that there is just a blind spot where fetuses are concerned, even wanted fetuses, and they are just not protected in the way that adult Americans are protected. There is a blind spot. You have really hit upon a major problem. We have a vote on the floor and let me say to our other witnesses who are scheduled. We are going to move this hearing along even if it means foregoing some of the questions that we really want to ask Ms. Haire. We will recess for just about 8 minutes and then we will come back and finish up our questions and move onto the next witness.

[Brief recess.]

Mr. GORE. The subcommittee will come back to order. On page 8 or 8½ of your prepared testimony, you note that the warnings about one of the commonly used drugs in labor is placed way down in the label for the physician, in the "Allergic Reaction" section. You called that to the attention of the FDA and noted that it seemed inappropriate treatment of such serious warning. Yet they have done nothing about it. When did you bring that to their attention?

Ms. HAIRE. I would have to check. I have submitted as part of my testimony my presentation to the Anesthetic and Life Support Drug Committee and I believe it is in there.

Mr. GORE. We do not have that but you can supply that for the record if you wish.

Ms. HAIRE. It has been several years.

Mr. GORE. What is your reaction to those who say that a warning to mothers can sometimes lead them to decide not to accept medication even when the doctor is convinced that that is an irrational choice on her part and that the doctor ought to have the right to produce what he or she believes is a more rational decision on the part of the patient by selectively denying information to the patient which might produce what seems to be an irrational decision.

Ms. **Haire**. I have had mothers informed kindly and unkindly. There are all sorts of ways of presenting this type of information to women. I have never suggested that an honest package insert be the only exchange of information between the physician and the patient. If the package insert were truly honest and presented to the woman sometime during her pregnancy there would be ample time for her to question her obstetrician and discuss her concerns.

I am fascinated that everyone thinks clinic mothers are unable to understand information regarding their obstetric care. I write a lot of material for the third grade reading level. I find you can explain a lot of technical information in very simple language. I would be happy to work with any company that would like to develop a package insert for their product that would also discuss the risks discussed in the scientific literature. We keep a close watch on the scientific literature. While the information is very technical in the journals it can be explained in relatively simple ways. I think you would find many women would continue to take the drugs. But many women would not, and that is the important thing.

Mr. **Gore**. At some point the approach of denying them information for their own good just conflicts with the basic rights of a citizen in this country. That is the philosophy we have always used in this country, that people are capable of making rational decisions on their own and if you give them the information in the long run it will work out for the best. That philosophy it seems to me ought to be used in this case as well. Maybe I am wrong but it certainly seems that way.

Ms. **Haire**. There are probably more women and their children damaged by taking the drugs than women and their children who were damaged because they did not take them.

Mr. **Gore**. You indicate that some labels—reading from page 14 of your testimony—that some labels say "Safe use in pregnant women other than in labor has not been established." On other occasions language is used such as "this does not exclude use in obstetrics." A layperson would read that and conclude well they looked at the use in labor and obstetrics and they decide it is clearly all right, most mothers think that well, it is so near to the birth it does not have time to get into the fetus for any length of time. A woman may conclude that the drug is probably OK in labor and obstetrics, but that conclusion is just wrong, is it not?

Ms. **Haire**. It is "weasel wording." That is a former FDA commissioner's term for that type of wording.

Mr. **Gore**. I would use stronger language and just say that the implication is absolutely false, except I know the word "safe" is not defined by the FDA in the same way as it is defined in the dictionary. It is defined in terms of risks and benefits and what they are really saying there is that obstetricians use these drugs in labor so frequently that people are convinced that the benefits are enormous in obstetrics. Since we know so little about the drug effects, it is probably right to conclude that people believe that when there are enormous benefits reported by obstetricians and a lot of uncertainty about the undesired effects, it sounds like the drugs are safe. That is really what people are saying, is it not?

Ms. **Haire**. Yes.

Mr. Gore. But it may or may not be true.

Ms. Haire. The FDA seems to think it can determine benefit/risk factors. There is no way that the FDA can determine what risk I am willing to take for the benefits I wish to receive. Rather than use the word "safe" I would much prefer to see FDA use the term "relative risk" or relative safety. The former legal counsel for FDA, Bill Vodra suggested that the FDA use the word "risk," rather than safety.

Mr. Gore. Are there any drugs on the market now that you think should be withdrawn under that kind of risk/benefit analysis?

Ms. Haire. I testified at the FDA hearing on Bendectin and I feel that there is insufficient data to support the safety or the risk of Bendectin.

Mr. Gore. But the drug companies say it will cost money to tell the mothers, it will cost money to print the information.

Ms. Haire. If they had any idea of how much money it is going to cost them not to, they would agree to print them. We are keeping a record of all of the information that goes into these package inserts. We are very conscious of the assurances of safety that are being made by the manufacturer.

Mr. Gore. There are two levels on which the issue is addressed. One is risk/benefit analysis itself and the second is informing of the patient or the mother. The FDA had difficulty dealing with the risk/benefit analysis in this area, but with specific regard to Bendectin the FDA made a public commitment to at least give the information to mothers so that the mothers could make the risk/benefit analysis on their own. But then the large pharmaceutical companies came in with the transition team between administrations and expressed their concern that this was going to cost them some money to print the information so that mothers would have it available. So the public commitment on the part of FDA to inform mothers of the risk they face and the risk faced by their unborn children has now been withdrawn. I happen to have a great deal of respect for the new commissioner at FDA. I think he is one of the bright spots in this administration, but I know that he and others at FDA have a difficult time balancing the various concerns and pressures which are brought to bear. I have been impressed with the way he has done that so far. I would not be at all surprised to see the FDA renew its commitment to a PPI for Bendectin and initiate a new approach to risk/benefit analysis where fetuses are exposed to the danger of birth defects from drugs used during pregnancy. But we will have to wait and see whether that does, in fact, occur. I am optimistic. I yield to my colleague.

Mr. Shamansky. I want to establish the distinction between the acceptability, in your mind, of the FDA saying, generally speaking, there is a good risk/benefit based on the information we have, as distinguished from telling the individual recipient of that that this decision applies in your case. There is still room for informed consent even if FDA said, generally speaking, the risk/benefit based on the information we have or anything we know about is acceptable.

Ms. Haire. The information in the package insert is not current, in my opinion, with the data available in the scientific literature.

Mr. **Shamansky**. Assuming the currency of the information.

Ms. **Haire**. In the Anesthetic and Life Support Committee presentation I recommended that four important sentences should be included in the package insert when applicable. These are:

> (a) No well-controlled long-term followup has been carried out on individuals exposed in utero to the effects of this drug. There may be delayed, long-term adverse effects on subsequent physical, neurologic, and mental development which cannot be determined at this time. (b) Physicians are not required to report an adverse drug reaction tothe FDA; therefore, there is no way of determining the exact rate of adverse drug reactions to this drug when it is used in non-research-obstetric care. (c) Since even the short-term direct and indirect effects of this drug vary with the individual physiology of each mother and her unborn child, the term "overdose" as it applies to the fetus cannot be defined for this drug.

Most people assume that if there is an adverse drug effect the doctor will have to report it to the FDA. That is not true. Only when the physician reports an adverse drug effect to the manufacturer must the manufacturer, in turn, report it to the FDA.

Mr. **Shamansky**. I am glad you mentioned that. I still want to pursue with you the idea—it seems to me a two-tiered thing, whatever FDA is eventually required to do. There is that generalization based on whatever data it has and then perhaps, in my mind, a requirement or a need to inform the particular patient so she could make the informed consent.

Ms. **Haire**. What we have asked the FDA to do is require the manufacturer to put in the package insert, whenever appropriate the words which are "No well-controlled long-term followup has been carried out on individuals exposed to the effects of this drug in utero. There may be delayed long-term adverse effects which cannot be determined at this time."

Mr. **Shamansky**. But is it fair to say, though, that at some point the FDA could make a general statement as to what it has found in order to inform the physicians all over the country what it knows? Then there is still an additional step before the safeguard applies to the individual.

Ms. **Haire**. Yes. There is information regarding obstetrics in many of these package inserts. It is insufficient information even for the physician. I feel physicians have been misled into a false sense of security with some of these products.

Mr. **Shamansky**. We are not zeroing in on something. Please be patient with me. On the risk benefit, I am assuming some place or other that there is a legitimate role for the FDA in making an assessment as best it can, for the determination of risk benefit.

Ms. **Haire**. Yes, but certainly the type of research FDA is requiring now is inadequate to demonstrate risk benefit.

Mr. **Shamansky**. I am excluding what it is doing now. I am just talking about a function. It is conceivable that using the most up to date acceptable standards, standards acceptable to you, whatever you require, there could be a point at which FDA could legitimately say we find the risk benefit OK. That does not apply to the individual person taking that drug. It merely is a statement by FDA to the medical profession and, therefore, to the company that the risk benefit they found acceptable. John, could you respond.

Ms. **Haire**. My response would be "yes." There is a legitimate function in FDA in approving the drug for a specific use to make that risk-benefit analysis. However the next step would be to be sure there was adequate disclosure of what risks were evaluated in the process. That disclosure should be made not only to the physician but, in the case of obstetric-related drugs, that disclosure should also be made to the parents of the child before the drug is administered.

Mr. Gore. Will the gentleman yield.

Under current procedure most of those analyses are performed by the manufacturer. Is that correct?

Ms. Haire. Yes.

Mr. Gore. And the testing protocols and the design of the study is not made available for analysis is that correct?

Ms. Haire. Correct. That information is not made available for analysis by consumer groups or responsible people on the outside.

Mr. Gore. It is made available to the FDA, John. I presume if they want it they can get it. Whether they get it or not I do not know, but in most cases the FDA is taking the word of the manufacturer for the whole thing.

Ms. Haire. That is correct as I understand it.

Mr. Gore. We will explore that with other witnesses. There may be some disagreement about that.

Mr. Shamansky. I have an important question. Again the lawyer pops out. On page 29 of your prepared testimony, Doris, there is what seems to me a very sweeping statement. At the top of the page the testimony says "With respect to effects on exposed offspring, then the Federal Government must also be held responsible for the care and compensation of those individuals injured or harmed by that drug or device." That is a big statement.

Ms. Haire. A "full disclosure" package insert can protect the company, the doctor and the Federal Government, as well as the patient. For the Federal Government to approve the package insert of a drug which does not clearly identify the risk of that drug is a irresponsible.

Mr. Shamansky. Are you suggesting the Government then becomes the insurer of the use of that drug?

Ms. Haire. I am saying that the Government has a responsibility to the public to see that the risk of a drug—and one of the risks is the areas of uncertainty—is discussed in the package insert of the drug that goes to the physician. I would again say that the Government has a responsibility to the public to see that manufacturers are required to produce a package insert that fully informs the patient, to every possible degree, of the possible risks.

Mr. Shamansky. Let me concede that but that is not the same as saying the Government then becomes the insuror. You say the Federal Government required the manufacturer to do that. In the event the manufacturer does not do that or somehow there is a mistake made does it follow logically that the Federal Government is then the insuror? Is the Government then liable for what the people down the chain might do or not do?

Ms. Haire. In my opinion the Federal Government, is the insuror of safety of drugs approved as safe by the FDA.

Mr. Shamansky. I hope you understand that I feel that is an element we have not heretofore had directly. I am sure we would both agree that is not now the law and it would be a significant departure from practice here.

Ms. **Haire**. The reason I feel these package inserts are so important is because of future interpretations of the law.

Mr. **Shamansky**. I am not denigrating the importance of the package. I am asking about the significance of who then is liable, is the Government neglectful. Should it be charged with neglect?

Ms. **Haire**. In my opinion, the Federal Government and the FDA are responsible for the harm caused to individuals damaged by drugs that have been approved by the FDA as safe. The dictionary definition of safe is free from harm or injury. I think the Food and Drug law should be amended so that the word safe is avoided.

Mr. **Shamansky**. But is there such a thing as safe in the clinical sense, is anything totally safe in a laymen's terms?

Ms. **Haire**. Nothing is safe in the term of the definition used in the dictionary. That is why I feel safe is an inappropriate word.

Mr. **Shamansky**. I am not suggesting that there is not a lot to be done with disclosure, better studies in this and that. Again I respond very specifically to your suggestion, on page 29 of your prepared statement that the Government be held responsible for the care and compensation of any individuals injured or harmed by an obstetric drug or device.

Ms. **Haire**. This is why we feel a simple statement saying that the long-term effect of this drug or device on human development is unknown would do a great deal to make people think, both the physician and the patient.

Mr. **Gore**. Mr. Volkmer.

Mr. **Volkmer**. No questions.

Mr. **Gore**. Thank you, Mrs. and Ms. Haire. We appreciate not only your testimony here this morning but the dedication you have shown to this issue for so many years.

Ms. **Haire**. We appreciate the opportunity.

Mr. **Gore**. I would like to call now Dr. Kenneth Ryan who is chairman of the department of obstetrics and gynecology at Harvard Medical School, and Dr. Yvonne Brackbill, professor of psychology at the University of Florida. We would like both of you to come up and appear as a panel. Let me note for the record that Dr. Ryan in addition to being chairman of the department of obstetrics and gynecology at Harvard Medical School also serves as chairman of the National Commission on Research and Human Subjects. Dr. Brackbill is also the author of a major new study on informed consent. For those wishing a road map of sorts to this hearing let me say that is the panel on bioethics and informed consent. We felt in analyzing this issue that we ought to explore this aspect of it early on. We will begin with you Dr. Ryan. Without objection the prepared statements of both witnesses on this panel will be put in the record. We invite you to proceed with your presentation.

[The biographical sketch of Dr. Ryan follows:]

BIOGRAPHY

WITNESS TO COMMITTEE ON SCIENCE AND TECHNOLOGY
UNITED STATES HOUSE OF REPRESENTATIVES

JULY 30, 1981

Kenneth J. Ryan, MD

Professor and Chairman, Department of Obstetrics and Gynecology; Director, Laboratory of Human Reproduction and Reproductive Biology, Harvard Medical School, Brigham and Women's Hospital

75 Francis Street
Boston, Massachusetts 02115

Medical Education

1948-1952 Harvard Medical School
MD Magna Cum Laude

Residency Training in Medicine, Fellowship in Biochemistry

1952-1957 Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Columbia Presbyterian Hospital, New York, New York

Residency Training in Obstetrics and Gynecology

1957-1960 Boston Lying In Hospital, Boston, Massachusetts
Free Hospital for Women, Brookline, Massachusetts

Academic Positions

1973-present Professor and Chairman, Department of Obstetrics and Gynecology, Harvard Medical School

1970-1973 Professor and Chairman, Department of Obstetrics and Gynecology, University of California at San Diego

1961-1970 Professor and Chairman, Department of Obstetrics and Gynecology, Case-Western Reserve University

1960-1961 Instructor in Obstetrics and Gynecology
Director, Fearing Laboratory, Harvard Medical School

Public Service and Professional Activities

1968-1971 President's Committee on Mental Retardation

1969-1971 Member, National Advisory Council, National Institutes of Child Health and Human Development

1974-1978 Chairman, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

1971-present Member, Institute of Medicine of the National Academy of Sciences (Council 1981)

STATEMENTS OF KENNETH RYAN, CHAIRMAN, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, HARVARD MEDICAL SCHOOL AND YVONNE BRACKBILL, PROFESSOR OF PSYCHOLOGY, UNIVERSITY OF FLORIDA

Dr. RYAN. Thank you. I appreciate being invited to discuss drug use in pregnancy and bioethics. Before speaking specifically to issues on bioethics, I would like to say several things with respect to the need for the use of drugs during pregnancy because it is pertinent not only to clinical management of patients but also to ethical considerations. I have divided drug use into two types, which I designate as discretionary and nondiscretionary. Discretionary use is defined as the use of a drug for a nonhealth threatening or nonlife threatening condition where suitable alternatives exist including avoiding drugs entirely. This includes the use of many over-the-counter drugs. We have been talking about what physicians prescribe, but patients also self-medicate themselves creating a flourishing over-the-counter drug industry. Very often patients use drugs for minor or self-limiting symptoms, but I also include discretionary use of drugs for relief of pain during labor and delivery when need is not established in an individual case. In other words I believe that physician and patient discretion should be used during the birth process and one should not assume that all patients are going to receive pain medication or anesthesia. On the contrary, I think patients should be prepared for the alternative.

During prenatal care, the kind of symptoms for which drugs are used include: morning sickness, headache, common colds and allergy. In the experience of a physician one probably has more inquiries about the safety of the over-the-counter drugs for which there is little information on risk. There is very little data about the common drugs that anyone can go out and buy and use during pregnancy without a prescription. There may be an admonition to ask the physician but there is a limit to what the physician knows.

I would define nondiscretionary use of drugs, as the use of medicines for serious medical problems where the health and life of the mother is in jeopardy. When that is the case the fetus is also in jeopardy. This includes: systemic infections, hypertension, diabetes, seizure disorders and psychiatric problems where drug use is often not discretionary. They have to be used for health and safety of the mother and the baby. It makes a big difference which kind of indication you are involved in when you start discussing the question of the kinds of risk one might assume.

Regardless of the indication for drug use there are several caveats which should be controlling and other witnesses will doubtless say the same thing. Most drugs given the mother reach the fetus. Pharmacological effects of drugs are most difficult to predict the younger the fetus and that is why drugs should be avoided early in pregnancy. The risks of serious harm have been ascertained with only a few specific drugs. When I use the word ascertained I mean established beyond a reasonable doubt. There are a lot of unsubstantiated claims. You have heard reference to Bendectin and the claims and counter-claims are confusing not only to the public but to the physician. Risk data are most helpful when they are positive. I do not think it helps a patient to say the risks are unknown because then they are left with a cloud hanging over their head. If risks are unknown we should be aware of it but it is distressing when for instance I have a woman with rapidly rising blood pressure and have to use a drug for which the risks are unknown When the incidence of adverse risk is low—and Dr. Slone will speak about this when he covers the quality of epidemiological studies, when the incidence of adverse effect is low or there is a long time lag as with diethylstilbestrol, one can completely miss a possible risk.

Mr. **Gore**. That is DES?

Dr. **Ryan**. Diethylstilbestrol. DES is a synthetic steroid. To summarize, I do not think a drug should be used in pregnancy unless its efficacy is known or can be reasonably ascertained. We know aspirin cures headaches. If we know that and a woman wants to take it for a headache she can make that decision. I do not think, however, that we should use drugs for symptoms for which the efficacy of a drug is not established because then one is taking an unconscionable risk for an unknown benefit. That is not stressed enough. I will come to this later under ethical considerations but before drugs are used in pregnancy they ought to be demonstrated to be efficacious in the nonpregnant state. We cannot start trying to determine efficacy for the first time in pregnancy.

An unexpected pregnancy must also always be considered before medicines are prescribed. We are trying to avoid X-rays during pregnancy. We are trying to avoid all kinds of medications during the first trimester of pregnancy. Unless the doctor thinks about the possibility of a pregnancy and, unless the patient herself thinks about it there may be problems, and an unplanned risk to the fetus. I would like to say a word about teratological effects and perhaps clear up one confusing point that you referred to, Congressman Gore. Five percent of all live births result in anomalies, About half of these anomalies are major. It is only 3 to 5 percent of the 5 percent that have been attributed to drugs. We know very little about the risks of neurobehavioral problems due to drugs taken during labor and delivery. I have seen little good data on risks for drugs taken later in pregnancy. The reason the incidence of anomalies is reasonably accurate is that these defects are not ordinarily missed and the Center for Disease Control has a congenital malformation surveillance which monitors occurrence in selected places around the country. I point that out when you consider supporting the CDC in the future.

Mr. **Gore**. We will put that in the record.

Dr. **Ryan**. I would like to put it in the record because what we are talking about here—getting adequate data. I do not think any witness that is going to speak before you today will say we should not have more adequate data. And we have to strengthen those resources within our system that can obtain it. I talked about teratological effects in general but I would like to respond to your specific questions with respect to those drugs in which a risk is reasonably well known.

There are only a handful which incude: Thalidomide, a sedative, Warfarin, a blood anticoagulant, also called Dicumarol. Ametitopierin, a drug used for leukemia. Hydantoins, anticonvulsants, and of course diethylstilbestrol, a hormone. These are the drugs we know produce defects. In most instances there is little indication for their use. But I should point out that we have pregnant patients who have leukemia and we have patients with seizure disorders that need medication. In some instances we have to rely on drugs which pose a risk to the child. There you have very little discretion.

Most prescription and over the counter drugs have not been associated with specific tetrogenic effects. The data for Bendectin the antinausiant has been covered in the newspapers but the data on adverse effect is weak, epidemiological studies have not demonstrated specific teratological effects in the same way that I described for the drugs listed above.

I would like to go on with neurobehavioral and developmental effects of drugs. Dr. Brackbill is here and she will also speak to this. I do not want to preempt her comments but I should say one or two things that are important, because Doris Haire on page 4 of her testimony says there is no doubt in her mind a significant proportion of 4 million children are afflicted with mental and neurological dysfunctions due to drugs. There may be no doubt in her mind but there is doubt in a lot of other peoples' minds and we should get facts before making such statements. I should point out to you that there are such things as rubella, hypertension, maternal infections, smoking, alcoholism, maternal socioeconomic class and education which have been demonstrated to be associated with poor fetal outcomes. You cannot simply ask someone who has such a pregnancy history did you receive medication? You want to know whether the pregnant woman smoked or whether or not she drank. We all know about the alcohol syndrome. Of all the things we will talk about today more children are affected by maternal smoking during pregnancy, than by drugs and when we get to the ethics issue we should ask about the posture of the Government with respect to the tobacco industry. Almost every study has shown increased spontaneous abortion, prematurity and lower birth rate in association with smoking during pregnancy. This is something we can do more about. Neurobehavioral developmental effects can be attributed more to other factors, such as fetal anoxia than to drugs. One percent of all pregnancies have antepartum bleeding, which can also contribute to fetal problems. When the mother has that kind of condition she may well receive drugs and it is impossible to decipher whether the indication for the drugs caused the problem or the drugs themselves. Tetracyclines, given for infection in the pregnant woman may discolor teeth or affect bone growth of the fetus. Drugs to treat thyroid disorders may cause fetal goiter even if taken later in pregnancy so there are some drugs used for legitimate medical purposes which can cause fetal defects. What Mrs. Haire and Dr. Brackbill refer to is the relationship of drugs used for labor and delivery, to neuro-behavior defects in newborns, which is less certain. This has been the subject of FDA hearings. The quality and completeness of those hearings are up for discussion today. In Mrs. Haire's testimony she did refer to Dr. Brackbill's research and said that they demonstrated certain things. I would like to point out that the work is controversial. I am not going to make any further comment except to say there are a lot of people who do not agree with the conclusions reached or the methods used by Dr. Brackbill. It is difficult for the Congress, lay people and even doctors to know who is correct based on newspaper accounts. One of the reasons the Brackbill study was criticized is because of lack of control of confounding factors such as the maternal disease I referred to.

I would like to say a word about ethical issues. We think of ethical problems as somehow being mystical. A lot of ethical problems would disappear if we could get our facts straight. Unfortunately getting facts straight is an ethical problem. People present "data" which is not what it appears to be. This poses an ethical issue because then you make decisions, on erroneous assumptions, ethical issues arise when the safety and/or comfort of the pregnant woman is pitted against risks to her unborn child. Naturally, when drug use is nondiscretionary—essential—the problem is selection of the right pharmaceutical agent to be used, and minimizing risk by appropriate dosage and timing. If a mother is ill the fetus does not benefit by withholding treatment so it is with the drugs that we have to use for serious problems that we need the most information to minimize risk. I agree with Doris Haire and the women's movement who want the public educated about drug use. The health profession also needs to be educated and we should avoid risks by avoiding unnecessary drug use. That is difficult because we are a drug-taking society. There are symptoms and illnesses that are self-limiting and need no drugs. Ethical concerns of society are expressed in terms of demand for drug testing and labeling to insure when medicine is needed that the safest type and dose are utilized.

With respect to the kind of studies that should be done, it is obvious that animal studies in subhuman primates cannot substitute for seeing what a drug does in the human. I feel that drug testing can be ethically conducted during human pregnancy if investigators adhere to principles of respect for human life, beneficence and justice. That is the message of the Belmont Report of the National Commission which was sent to Congress. The most frustrating problem is to treat a pregnant woman for a serious disease and find that the drug used has not had safety in pregnancy established. I would urge that we get as much information as possible on those kinds of important drugs. In the early work of the commission, a lot of people were concerned about research on aborted fetuses but in point of fact our recommendations covered other situations involving therapeutic research directed to the pregnant woman and her fetus. That is of more concern to us in the present hearings. Ethical research can and should be done. We even urged the Secretary to sponsor such research. When I refer to therapeutic drugs I am covering situations of potential beneficial effect to the mother.

With respect to the FDA, I think they have done a tremendous job since the Thalidomide tragedy, in testing drugs on pregnant animals and testing efficacy of drugs. The FDA covers postmarketing surveillance, but it is not as good as it should be. Package inserts help educate the public. I supported the FDA for package inserts and I think they should be continued.

Mr. GORE. You supported the——

Dr. RYAN. When the FDA was being sued by the American College of Obstetricians, I supported FDA on the question of package inserts for estrogens for menopausal women and I believe package inserts should be included whenever possible.

Mr. Gore. You supported their prior position?

Dr. Ryan. Yes. But I should point out to you that the inserts that are included with the drug for patient and physician use have to be factual. They have to be timely and they have to be readable. Investigators are studying whether or not the ones that have been put in with drugs are helpful. I do not know whether we have done all we can by just providing the package insert. The question is when the information should be given. If it is a pregnant woman one should not wait until she is in labor and delivering before discussing any of these drug issues. Drug information is part of prenatal care. The whole range of medicines a woman might take should be discussed ahead of time.

Mrs. Haire made an assertion as to the kinds of pressures—physicians are under but I am under none of the constraints that she talked about. We do not condone teaching practices which are not optimal for patient care. We are not trying to hide the truth about neurobehavioral effects of any drug.

Mrs. Haire had a comment in her testimony about ultrasound and I should point out she used the word radiation which I hope people will realize is not incorrect. There is a difference between ultrasound and radiation. She may want to correct the error. If she has any information that is factual with respect to ultrasound I would like to see it. I have never seen convincing information with respect to adverse effects of ultrasound. I think the risk of ultrasound is unknown.

Mr. Gore. Has the appropriate research been done to answer that question?

Dr. Ryan. It is still in progress. I hope the Government suports research on the outcome of children that have already been subjected to ultrasound. I believe that is going on, but adequate animal studies have not been done. With ultrasound you can cook things. Damage depends on frequency and intensity so I think adequate studies have to be done. Ultrasound is used widely—Lord knows we do not want another DES tragedy.

I think discretionary drug use at any time during pregnancy should be discouraged. If you do not have to use a drug, do not. That includes labor, delivery, and throughout the entire pregnancy. That is therapeutic nihilism to be sure, but There will always be patients that are going to have a headache so severe they have to take something for it.

Mr. Gore. Do you think discretionary drug use during labor should be discouraged by physicians?

Dr. Ryan. Yes, I think we should.

Mr. Gore. Do you think it is?

Dr. Ryan. Yes, in some instances.

Mr. Gore. Do you think most physicians discourage it?

Dr. Ryan. It is hard to respond to that kind of question. Let me say that there has been a change in the use of such drugs even in our own hospital which is the largest obstetrical unit in New England to a point now where about half the women have no——

Mr. Gore. Is it not true there are more drugs being prescribed during pregnancy today than in the past?

Dr. RYAN. I do not have that information.

Mr. GORE. I think we will have testimony from Dr. Jaffe later on that indicates precisely that, in spite of the conclusions that emphasis in the field—and you are as distinguished as any in the entire country or world for that matter—despite the conclusions that you have reached and have just enunciated that doctors should discourage drug use during pregnancy, the fact is that more drugs are being prescribed during pregnancy now than ever before.

Dr. RYAN. Well if that is true it is unfortunate and sad. I would like to see what the drugs are and what they are used for but it certainly is nothing that I would support. That is why I made the important distinction between discretionary and nondiscretionary drug use, so that discretionary drug use should be discouraged. If drugs are used they should have their efficacy established in the nonpregnant state. I can give an example. One of the drugs has been established as antiasthmatic in men and women who are not pregnant—I have a pregnant patient on that drug because she is asthmatic and cannot be without it. There is however nothing established on the safety of this particular drug in pregnancy. The existence of unsuspected pregnancy should always be considered before drugs are utilized and I cannot emphasize that enough. During active reproductive life women have to consider this and we should educate them and educate physicians. Drugs that are specifically designed for use in pregnancy should be extensively studied in appropriate test systems and finally in human pregnancy before and after marketing. If you do not do that these drugs will creep into use and you will not have the safety and the risk factors being asked for. Drugs that have important applications to medical needs in pregnancy but are not specifically designed for that purpose should also be identified and specifically tested for such use. Again if we do not do that they will creep into use. They will be FDA approved drugs but not approved for that indication or specifically for use in pregnancy. Finally, appropriate congressional support to the FDA and to such data-collecting agencies as the centers for disease control must be provided if their objectives are to be realized. If you are to get something more out of FDA you are going to have to look at their budget. Even in times of fiscal restraint the most cost-effective benefit to society is still prevention of disease and disability at the beginning of life. Finally the root of all ethics in trying to deal with this issue, is to try and sort out the facts from the suppositions and to get honest ethically based information. I have heard about the suspect motivations of doctors, with implication that someone who is a nonphysician lobbyist has only altruistic motivations. Most of the time motivations are honorable on both sides but I think that physicians are a heterogenous group of people who are concerned about the health and welfare of their patients and I resent blanket statements to the contrary. The comment that the FDA and obstetricians do not want information released on drug studies is not an adequate defense against sloppy research.

Thank you.

[The prepared statement of Dr. Ryan follows:]

TESTIMONY OF KENNETH J. RYAN, MD

COMMITTEE ON SCIENCE AND TECHNOLOGY
UNITED STATES HOUSE OF REPRESENTATIVES

JULY 30, 1981

Drug Use During Pregnancy

Drug use during pregnancy occurs under two types of circumstances, discretionary and nondiscretionary, which pose different medical and ethical concerns. Discretionary use is defined as administering drugs for "nonhealth" and non-life-threatening purposes during pregnancy where suitable alternatives for avoiding them exist This would include use of many over-the-counter drugs, treatment of relatively minor self-limiting symptoms, and even use of drugs for pain relief during labor and delivery when their need is not established in an individual case.

Nondiscretionary use, in this context, would involve treatment for more serious medical problems where the health and life of the mother (and often the fetus) are in jeopardy. Such medical problems which may be present during pregnancy include: systemic infections, hypertension, diabetes, seizure disorders, and psychiatric problems. Relief of pain and anesthesia during labor and delivery may be nondiscretionary when the process is prolonged or complicated.

The importance of making the distinction between the two indications for drug use will become crucial in relationship to the known or unknown risks we might reasonably assume in providing relief to the mother. In either type of drug use, several caveats should be controlling.

Most drugs given to the mother cross the placenta and reach the fetus. The pharmacological effects of a drug are most difficult to predict and drugs should be avoided, unless essential, during embryonic development (first trimester). The risks of serious harm from drug use in pregnancy have been ascertained in only a few cases, and risk data are most helpful when positive. It is difficult (if not impossible) to exclude all risks. Adverse effects can be missed unless specifically sought, and when the incidence of an adverse effect is low, or a long time lag exists (as in diethylstilbestrol), studies may be misleading. A drug should not ordinarily be used in pregnancy unless needed and its efficacy is known. The existence of an unsuspected pregnancy must always be considered before medicines are prescribed.

Teratological Effects

Some form of congenital anomaly occurs in about 5% of all live births (the rate is higher for miscarriages), and this translates into approximately 150,000 cases of birth defects each year in the United States. While many of them are of a minor nature, fully half, or more, of the anomalies involve major defects affecting the fetal central nervous system, heart, musculoskeletal system, and gastrointestinal tract. Such defects involve major medical problems, human suffering, and cost. In only rare instances can anomalies definitely be attributed to a drug, the vast majority of cases being of genetic or unknown environmental cause. Some of the drugs known to cause serious human defects include: thalidomide (a sedative), warfarin (a blood anticoagulant), aminopterin (an antileukemia drug), hydantoins (anticonvulsants), and diethylstilbestrol (a synthetic steroid).

The adverse effects of these drugs are well known, and some should never be used in pregnancy. The nondiscretionary (essential) need of others is rare, involving only serious medical problems such as thromboembolism, leukemia, or uncontrolled seizures. Clearly, some kind of risk/benefit assessment would be necessary before ever considering their use.

Most drugs (prescription and over-the-counter) have not been associated with specific teratogenic effects when epidemiological surveys have been conducted (JAMA 248:343-346, 1981). The difficulty in excluding all risk, however, has already been alluded to.

Neurobehavioral and Developmental Effects of Drugs

Neurobehavioral development and physical growth of the newborn and child are highly variable and subject, in an unpredictable way, to the effects of prenatal factors including maternal health, infection, smoking, alcohol consumption, socioeconomic class, and education.

Peripartal factors such as fetal anoxia, difficult delivery, and nursery care also may adversely affect the newborn. The establishment of the normal range of neurobehavioral development itself is not perfected, so that it has been quite difficult to identify and attribute adverse effects to most drugs used later in pregnancy, let alone to any other specific factor.

Some drugs such as tetracyclines (antibiotics) may discolor teeth or affect bone growth, and drugs used to treat thyroid disease may cause fetal goiter, if taken during later periods of pregnancy. The relationship of the use of drugs for labor and delivery (hypnotics, anesthetics) to neurobehavioral effects in the newborn or growing child has been the subject of previous Congressional and FDA hearings (1979). Adverse risks, other than short-term pharmacological effects, have not been definitely established, and there is controversy over the adequacy of the studies available and the need for further investigation. There is an FDA subcommittee for review of this matter (Anesthetic and Life Support Drugs Advisory Committee).

Ethical Issues

→ Ethical issues arise when the safety and/or comfort of the pregnant woman is pitted against risks to her unborn child. Naturally, when drug use is nondiscretionary (essential), the problem is selection of the right pharmaceutical agent to be used, and minimizing risk by appropriate dosage. xLX (V)

It is largely in the discretionary use of drugs where education of the public and health profession can help avoid risk, simply by avoiding unnecessary drug use.

Ethical concerns of society also are expressed in terms of the demand for drug testing and labelling to ensure that when medicine is needed, the safest type and dose are utilized.

While animal (including subhuman primates) studies of drugs should precede human use, risk can be ascertained only after sufficient study in human pregnancy. Studies can be ethically conducted during human pregnancy if the investigators adhere to the principles of respect for human life, beneficence and justice. It would be unethical if studies are not performed, which thereby would deny availability of necessary drugs to women and their offspring.

The most frustrating problem for the physician treating a pregnant woman for a serious disease process is when the potential drug is labelled, "Safety for use in pregnancy has not been established."

The National Commission for the Protection of Human Subjects has submitted a report to the Congress on Research on the Fetus in 1975 (DHEW Publication No. (OS) 76-127), and although much public attention was directed at the time to research on the aborted fetus, the recommendations covered situations involving therapeutic research directed to the pregnant woman and the fetus, which is of more concern to the present hearings.

The FDA

The Food and Drug Administration has made great strides in terms of safety following the thalidomide tragedy. Drug testing in pregnant animals has become commonplace, efficacy of drugs must now be established, FDA reports cover post-marketing surveillance, and package inserts help in educating the public and profession. The FDA review process often is complicated by industry or public action lobbies which focus on narrow goals and are long on opinion, but short on data.

Progress in the area of fetal safety will depend on insistence on establishment of efficacy of any drug proposed, avoidance of discretionary drug use for "trivial" purposes, and insistence on testing in human pregnancy when it is likely that the drug will be needed for the protection of women, their pregnancies, or their fetuses. Better data-keeping on fetal outcome in cases of nondiscretionary drug use is needed.

Conclusions

1. Discretionary drug use at any time during pregnancy should be discouraged.
2. The existence of an unsuspected pregnancy should always be considered before drugs are utilized.
3. Drugs that are specifically designed for use in pregnancy should be extensively studied in appropriate test systems and in human pregnancy before and after marketing.
4. Drugs that have important application to medical needs in pregnancy, but have not been designed or marketed

> for that purpose, should be identified and specifically tested for such use.
>
> 5. Appropriate Congressional support to the FDA and to such data-collecting agencies as the Centers for Disease Control must be provided if their objectives are to be realized. Even in times of fiscal restraint, the most cost effective benefit to society is still the prevention of disease and disability at the beginning of life.

Mr. **Gore**. Thank you. I know that you have that reaction to some of the statements that our previous witness made, but I think that others have allowed the reaction to speculation about motives to lead them to reject some of the accurate conclusions in other areas that Mrs. Haire has evidently reached.

Dr. **Ryan**. I agree with many of the recommendations she has made. I am not really quarreling about the fact that FDA should be accountable for specifying drugs that are approved for use in pregnancy and that risks ought to be identified.

Mr. **Gore**. It is not done now.

Dr. **Ryan**. I understand. I support those kinds of endeavors. Unfortunately we are coming from different directions.

Mr. **Gore**. Dr. Brackbill, welcome and please proceed.

Ds. **Brackbill**. Thank you, Mr. Chairman and members of the subcommittee for the opportunity to speak about teratogenic drugs and problems of informed consent in obstetric drug administration—a research area in which I have been involved for more than a decade.

The horrors experienced by patients and by subjects of experimental research in Nazi Germany focused world attention on the need to obtain explicit consent for both treatment and research participation. The doctrine put forth at Nuremberg has, as its first principle, that voluntary consent is absolutely essential. This doctrine, which has come to be called informed consent has three components: voluntariness, competence, and information. Of these, information is the most basic element: the consenter must be informed about the treatment or experiment and about the probable consequences of submitting to it. Without such information, informed consent is not possible.

Obtaining informed consent from pregnant women is particularly important because drug consumption during pregnancy and childbirth is particularly risky for the fetus and young child.

Let me clarify three points. The research demonstrating the adverse effects on the young organism of either acute or chronic doses of a large number of drugs is not controversial. FDA statisticians concluded that all of the drug studies—by now there are 45 alone on obstetric drugs not to mention the large number of animal studies—are all in basic agreement that there are adverse effects.

How long the effects last is a matter that is not known at present because there have not been sufficient studies on it.

In addition to this, let me point out something that has escaped our attention so far this morning.

Teratological effects include both structural and functional effects. That is both anatomical or morphological changes and behavioral effects.

There are some drugs that affect both function and behavior. There are others that affect only structure, and there are some that affect behavior only. At least with present techniques of histological examination, there are behavioral changes for which one can find no underlying structural change. The orthogonal effects of behavior and structure are something that was discussed at length in a lead article in Science magazine by Vorhees, et al. last year.

Another point that has escaped our attention and I think should be pinpointed now is that teratology is concerned not just with grossly identifiable changes, but with subtle effects, low level effects. Under those circumstances, the number of children affected by drugs administered preconceptionally, prenatally, perinatally, or postnatally before the CNS has finished its development is unknown. It certainly is higher than 5 percent, however.

At any rate, to illustrate the importance of teratological drugs in the United States, for example, aspirin is consumed at the rate of 18.5 tons a day and Valium at the rate of more than 8,000 tons a year.

Both aspirin and Valium are well documented teratogens. But how many pregnant women know this? And how many women consume aspirin or valium during their pregnancies?

My colleagues and I are currently studying drug exposure during pregnancy and childbirth; the status of those drugs with respect to adverse effects, safety, and FDA approval for use in childbirth; and the amount of information mothers have about the drugs to which they have been exposed.

Subjects to date have been 304 randomly selected postpartum inpatients who delivered clinically normal babies. This average age is 22.5 years, and average education, 11.2 years; 36 percent are employed outside the home; 49 percent are white; 51 percent black; 49 percent are parity 1; 51 percent, parity 2 or more.

We obtain data on drug exposure and drug information by interview and from medical records. We score drug information according to consumer information standards adopted by the American Society of Hospital Pharmacists.

These are shown in table 1 of your handout.

Our results show that during pregnancy mothers consumed 93 different prescription and over-the-counter drugs. A review of the literature was conducted for each of the 93 drug products to determine its status with respect to adverse drug effects. Of the 93 drug products which mothers reported consuming during their pregnancies, 47 percent contain one or more ingredients with documented adverse effects.

As shown in table 2, almost half of the mothers consumed at least one such documented drug. Even worse to consider is the fact that 70 percent of the drug ingredients mothers consumed during pregnancy apparently have no published reports of their safety or lack of it, so their status with regard to adverse effects is unknown.

Therefore, our results may seriously underestimate the true exent of teratogenic exposure.

During labor and delivery, mothers were administered 43 different drugs. Sixty percent of these obstetric drugs have been found to produce adverse effects on offspring, according to previously published research.

As shown in table 2, 85 percent of the mothers received at least one teratogenic drug during childbirth, and 64 percent received at least two. Of the 15 most frequently administered obstetric drugs, 10 are teratogenic or toxic, according to published research. Of the remaining five, four apparently have not been studied with respect to adverse effects.

Considering all the drugs prescribed during pregnancy, labor, and delivery, how many have the FDA actually approved for those uses?

After checking first with the Physicians' Desk Reference and then with the FDA, we conclude that only 1 out of 58 prescription drugs represented in this study has been approved for use in pregnancy, labor, and delivery.

The significance of this for informed consent stems from an FDA ruling of 1972 in which that agency very clearly and unambiguously stated that when approved drugs are used for nonapproved purposes, they once again assume the status of experimental drugs.

This means that when such experimental drugs are used on pregnant and parturient women, those women become experimental subjects and must give informed consent for experimentation as well as informed consent for treatment.

None of the mothers in our study had given informed consent for the administration of experimental drugs.

Now, let me turn to the information mothers had about the drugs to which they were exposed. As table 1 indicates, mothers knew very little about the drugs they consumed during pregnancy. Their mean prenatal drug information score was a mere 1.7 out of 9 possible points. Most mothers knew why they had taken a drug, for example, for morning sickness. Some knew the name of the drug. Few, however, could summon up more information about it.

Mothers rarely mentioned drug risks or alternatives to drug treatment.

These empirical data are in direct contradiction to Commissioner Hayes' opinion as stated on his testimony, page 6, that the FDA current mechanism for dissemination of information is generally effective.

Mothers had even less information about the drugs to which they and their infants were exposed during their labor and delivery. The mean obstetric drug information score was .33 out of 9 possible points. Failing adequate information, mothers are not giving and cannot give truly informed consent for treatment.

In summary, we are finding that mothers know very little about the medications they take prenatally and even less about the medications they are administered during labor and delivery.

Failing adequate information, a large number of babies are exposed to drugs with teratogenic or toxic potential. Adding to the gravity of this situation is the fact that two-thirds of the prenatal drug ingredients and one-third of the obstetric drug ingredients figuring in this study have no apparent, published documentation with respect to their teratogenicity or toxicity. When information is thus lacking, informed consent for treatment is also lacking.

Finally, with rare exception, most prescription drugs to which mothers and babies are exposed are experimental drugs in that they have not been approved for use in pregnancy, labor and delivery.

Under these circumstances, informed consent for experimentation is ethically and legally required. In practice, it is never obtained.

There are remedies for these problems. Among the potential solutions, I recommend the following for your consideration: My first recommendation, as I have testified before, stems from the fact that the mother is a consumer. She must be treated as an intelligent human being, capable of understanding information on drugs when it is written in plain English, capable of choosing alternatives to drugs.

Furthermore, she has the right to this information, just as a smoker has the right to know that tobacco is injurious to her/his health.

It is currently within the power of the Federal Government to achieve these goals.

The Department of Health and Human Services has two offices to deal with consumer information and education. One is the Office of Disease Prevention and Health Promotion. The other is the National Center for Health Care Technology.

I recommend that DHHS prepare two versions of obstetric medication information: one for the consumer and one for the professional.

I further recommend that the information be made available through the appropriate DHHS offices.

My second recommendation is that you request FDA to continue its program to require the informational brochures called patient package inserts to be dispensed along with the drugs likely to be prescribed for pregnant and parturient women.

This program, under development for more than 2 years, was shelved last spring when FDA apparently bowed to the lobbying efforts of drug manufacturers, physicians and pharmacists and to the antiregulation Zeitgeist of the present administration.

My third recommendation is that you encourage FDA to make available to consumers and health care providers a list of drugs approved for use in pregnancy, labor and delivery.

As we already noted, there is no such list at present.

My last recommendation is that you seek enforcement of existing sanctions against institutions and health care providers who fail to obtain informed consent for experimentation before using drugs in obstetrics that have not been approved for that purpose.

Thank you again, Mr. Chairman and members of the subcommittee, for this opportunity to speak to you about teratogenic drugs and problems of informed consent in obstetric drug administration.

[The attachment follows:]

TABLE 1

Drug Information to be Provided Consumers Policy Statement by the American Society of Hospital Pharmacists[a]	Number of Informed Women					
	Prenatal Drug Products[b]			Obstetric Drug Products[c]		
	N[d]	%(N/229)		N	%(N/243)	
1. Name (Trademark, generic, common synonym or other descriptive names(s))	145	63		6	2	
2. Intended use and expected action	222	97		15	6	
3. Route, dosage form, dosage and administration schedule	75	33		16	7	
4. Special directions for preparation and/or administration	6	3		1	1	
5. Precautions to be observed during administration	3	1		2	1	
6. Common side effects that may be encountered, including their avoidance and action required if they occur	4	2		1	1	
7. Techniques for self-monitoring of drug therapy	0	0		0	0	
8. Potential drug-drug or drug-food interactions or other therapeutic contraindications	1	1		0	0	
9. Prescription refill information; action to be taken in the event of a missed dose; any other information peculiar to the specific patient or drug	7	3		1	1	
			1.7*			.33*

---

[a] Modified from: Statement of Pharmacist-Conducted Pateint Counseling, *Am. J. Hosp. Pharm*. 33, 644, (1976).

[b] Definition of prenatal drug product does not include vitamins and iron.

[c] Definition of obstetric drug product does not include sudsy enema or dextrose in saline solution.

[d] N=Number of women who were informed about medications they had taken, e.g., 145 women knew the names of all prenatal products consumed.

*Mean Score Points

Table 2

Exposure to Drugs with Documented Adverse Effects on Offspring

No. of Adverse Drug Products	Prenatal Exposure (N-304) N	Prenatal Exposure (N-304) %	Perinatal Exposure (N-244) N	Perinatal Exposure (N-244) %
1 or more	144	47	209	86
2 or more	44	14	157	64
3 or more	10	3	106	43
4 or more	4	1	56	23

Mr. **GORE**. Thank you very much.

Mr. Shamansky?

Mr. **SHAMANSKY**. Thank you, Mr. Chairman.

Dr. Ryan, you have to catch an airplane, so we will try to move this on.

Please extend my respect to Dr. Freedman. This is an aside. Having taken care of that important business, I am still concerned about the apparent inability or the failure of the medical profession to address itself to the issue that we are talking about today.

Why hasn't something more been done. Why does it take Doris Haire's devotion for 10 or 15 years? The devotion of a lay person? Where is the initiative from the medical profession to cover the area that Dr. Brackbill has spoken of?

Is it just the inertia? Is that what we are dealing with?

Dr. **RYAN**. It is hard to say. I can't sit here and be a spokesman for the American——

Mr. **SHAMANSKY**. You are in a position to give us an opinion.

Dr. **RYAN**. I think it is a combination of things. Things change slowly. A lot of the studies that Dr. Brackbill did should have been done long before she pursued them.

They were the neurobehavioral followups of children for the collaborative study. They were stopped when we did not have enough money to continue.

It takes a long time to get the kind of information you want. People are creatures of habit. The medical profession changes slowly, but there is no question that the drugs that were taken and the things that were done in the 1950's are not what is going on in this country today.

The Doris Haires, the women's movement, informed consumer groups and public hearings have in fact changed things.

Things are not perfect yet, but they are in the process of change.

Mr. **SHAMANSKY**. But it seems to me that the Doris Haires are making the change and I am looking for that spark within the profession itself.

Where is the self-generating interest within the profession?

Dr. **RYAN**. It is a question of what in point of fact you are looking for. We don't generally come lobbying.

Mr. **SHAMANSKY**. That is the question. Why does the Government have to come in? Why isn't the profession beating our door down?

Dr. **RYAN**. It is a combination of things. For one thing, a lot of these individuals are busy doing work just like you are today. I have left an office of patients to come down to Washington. I think that we are making progress. FDA is much better than it was before the Kefauver hearings.

It is much better since the thalidomide tragedy. That is the process in the democratic system.

You need the public lobbyist to be quite strident to get people's attention.

Mr. **SHAMANSKY**. Can you tell me, does Harvard Medical School make a conscious effort to encourage its staff and its students to be aware of their responsibilities as to obstetric medicine usage—assuming that they do have a responsibility in this area?

Dr. **Ryan**. Again it is one of the things I try and do personally. Again I can't speak for a huge institution, but the answer is yes, we are trying to make the kind of changes.

Mr. **Shamansky**. Are you satisfied with your progress?

Dr. **Ryan**. I don't know that one should ever be satisfied. I am satisfied with the fact that since I came to our institution that we changed the law in Massachusetts to allow midwives into the State; that we have reduced the incidence of anesthesia use for routine delivery and I am sure Mrs. Haire will be pleased to know that we have a large corridor used for women in labor to walk around rather than being confined to bed.

I think these kinds of things are taking place. I am shocked by the news that more drug use is creeping into the system which I don't condone, but our sphere of influence is limited.

We would like to get more texts out that reflect the modern approach to obstetrical care and so on.

Mr. **Gore**. I am sure you heard Dr. Brackbill's statement that 85 percent of the mothers surveyed received at least one teratogenic drug during childbirth and 64 percent received at least two.

Dr. **Ryan**. I don't know what drugs she talked about. It probably included aspirin, which she considered teratogenic.

I listed the four or five drugs that I know are teratogenic in the human. There are a lot of animal studies which may or may not be relevant. We know vitamin A is a teratogen and we excluded the vitamins from any consideration at all.

Vitamin A is a teratogen in animals. There are specific differences that have to be taken into consideration.

Dr. **Brackbill**. The most frequently administered obstetric drugs—this is not unique to the University of Florida. I checked with other universities such as the University of Michigan, and it is very much the same.

In rank order of frequency, first it is dextrose and sodium chloride. Maalox, oxytocin, promethazine (Phenergan), Meperidine (Demerol), lidocaine, nitrous oxide, Fentanyl, anestine, curare, pentothal, nesacaine, atropine, magnesium sulfate, and halothane.

Dr. **Ryan**. We should be cautious here because Dr. Brackbill is using a more inclusive term for teratogenic than the one that is ordinarily used.

She would include a behavioral effect as teratogenic result of these drugs. I say the data on those drugs is limited.

Dr. **Brackbill**. Most of the studies are structural teratology studies and they include various aspects, including decreased birth weight, digital defects, abortion, cleft palate, delayed ossification, skeletal abnormalities and growth rate.

Mr. **Gore**. I don't want to get bogged down in definitions.

Dr. **Ryan**. I think the quality of the testimony is important. The thing I would submit is there is a confusion here when you use the word teratology in Dr. Brackbill's context and you quote for instance that oxytocin might cause a cleft palate, when the drug is not used at a time when it could cause cleft palate. It may cause something else later on. We don't have time, but there are deep-seated differences in terms of the scientific evidence that people are willing to accept.

Mr. **Gore**. We are going to get into those, but they make it all the more important for mothers to have available to them the best information so they can make an intelligent choice.

Dr. **Ryan**. You said in your letter, are those women therapeutically deprived? Are they therapeutic orphans?

You just have to ask the questions, what about aspirin? I agree tons of it are used. What am I supposed to say to a woman? I will tell you what I generally say.

Use during the first trimester of pregnancy should be avoided. If you can't stand your headache, take it.

Mr. **Gore**. What about the concerns raised by others, when you say that and when doctors generally say that the statement carries with it an implication that use of the same drugs in the second two trimesters is okay?

Dr. **Ryan**. The only thing you can say about its use in latter trimesters is they can't cause the same kinds of abnormalities. You can't presume they are okay.

Dr. **Brackbill**. Excuse me. The period of risk for both structural and functional teratogenesis extends well beyond the first trimester. Certainly for behavioral teratogenesis, until the point at which the central nervous system has stopped developing at its most rapid rate.

A recent study has been done and submitted for publication comparing the effects of nitrous oxide and haothane on mice. Acute administrations of the drugs are given to one group prenatally and to another group or just after birth. The effects on motor development, locomotion and motor reflexes are the same for the two periods of administration.

Mr. **Gore**. It seems to me the real question remains, do you or do you not warn the mother of known potential effects?

Dr. **Ryan**. The answer to that question is, you should. They should be informed.

I would include my caveat, however, I don't condone trivial use of drugs. That takes away part of the issue. If the benefit of the drug and the efficacy are tremendously important to the pregnant woman then I think you have something to work with.

I don't think we should discuss trivial use of drugs.

Mr. **Gore**. You answered the question yes we should warn mothers of the potential effects. Unfortunately the answer to the question, do we, is no. They are not warned today.

Dr. **Ryan**. I can tell you that efforts are being made. National foundations, such as the March of Dimes, so the Kennedys came on TV. You hear it over the radio. You asked how do you educate people. I think you have to pay attention to how people get educated in this country. They are informed over television.

I think efforts have been made by certain foundations that are concerned with birth defects like the March of Dimes, to try and educate people. Every time you have a public hearing and it gets in the newspaper, more people read it.

Mr. **Shamansky**. Are you satisfied with efforts by the Food and Drug Administration or Health and Human Services to educate the public?

Dr. **Ryan**. No, I think they could do more, but I am sympathetic to their problems. I have heard Donald Kennedy speak about this. I am sympathetic to the problems of the bureaucracy and funding.

Mr. **Shamansky**. I am sympathetic with funding too, but absent a program, what is there to fund?

Dr. **Ryan**. Good people. When I talked about the bureaucracy, I had in mind turnover of personnel and the kind of people you have doing these jobs. That is what there is to fund.

Mr. **Gore**. Let me compare two statements made by our two witnesses here.

On page 4 Dr. Brackbill states:

> When such experimental drugs are used on pregnant and parturient women, those women become experimental subjects and must give informed consent for experimentation as well as informed consent for treatment.
>
> None of the mothers in our study had given informed consent for the administration of experimental drugs.

On page five of your statement, Dr. Ryan, you say that:

> Studies can be ethically conducted during human pregnancy if the investigators adhere to the principles of respect for human life, benificence and justice. It would be unethical if studies are not performed which thereby would deny availability of the drugs to women and their offspring.

Now, the question of the necessity to inform women, it seems to me, is at the interface between these two statements.

Dr. **Ryan**. Let me clarify that. In the end it is ironic, but it is true I agree with most of the conclusions Dr. Brackbill comes to. We just come from a different perspective. I don't disagree with the recommendations she has made, but I think the point is that using each individual pregnant woman as an experimental subject does not generate the kind of information that you are talking about.

You need sophisticated studies prior to the fact that these drugs get into use where each pregnant woman becomes an experimental subject for her individual doctor and he has to say "This drug is not approved for use by FDA."

It was only recently that Ritodrine, a drug used to prevent premature labor, was approved while this drug was used in Europe years earlier. There is a certain slowness in the FDA, and medical progress goes faster than they. You get drugs getting into use when adequate studies have not been carried out.

Mr. **Gore**. Our next panel will talk at some length about Ritodrine, but could you state more specifically the parameters you think would have to be followed if such research using pregnant mothers in this way is to remain ethical and within human research regulations?

Dr. **Ryan**. I would refer you to our commission report, but I will summarize.

Mr. **Gore**. I read that last night.

Dr. **Ryan**. I would summarize because that was the first report we put out. Research in human pregnancy not only would be ethical, but should be encouraged in line with our discussions today. Drugs should be adequately tested in animals for teratogenicity including in subhuman primates. Drugs should be tested in adult men and women prior to being used in human pregnancy and drugs should be demonstrated to be reasonably safe and efficacious for the medical indicators proposed. Then that drug has a place in human pregnancy. Only after that time should one start the study in human pregnancy. The drug has already gone through an elaborate testing process, but you are not now testing whether it works. You know it works reasonably well. You don't know of any adverse effects, but now you want to see if any occur. That is the kind of study I think all of us are asking for.

Mr. **Gore**. I want to recognize Mr. Walgren, but I want to make a brief statement first.

It seems to me when a pregnant mother is involved, the fact that the fetus is put at risk ought to lead society and FDA, as the instrument of society, in this area to bend over backward to provide more information rather than less to the mother of that fetus in order that we protect the fetus against the possibility of the harm which results, but in fact that has not been the response of society or the response of the FDA.

We will pursue this more later. Let me recognize Mr. Walgren.

Mr. **Walgren**. Dr. Ryan, you indicate on page 2 of your testimony that a drug should not ordinarily be used in pregnancy unless needed and its efficacy—underline efficacy—is known. I have been trying to understand the relationship of Bendectin to the medical profession, and I understand this is an area that has been gone over.

On the other hand, at a recent session of an advisory committee on maternal and child health, Marian Finkel of FDA said for the record that "The effectivness of Bendectin in cases of severe nausea and not responsive to nondrug methods has not been established." That is a direct quote. It has not been established.

My question is, where are we on that issue, to your knowledge? It seems if you apply the statement that you make on the record, that you certainly would not encourage the use of that drug.

Dr. **Ryan**. I do not encourage the use of drugs during the first trimester of pregnancy, but I can tell you some patients are quite ill, and will take medication even if they are warned of potential risk.

Generally, if we have a patient that cannot cope we will hospitalize them for nausea and vomiting, but this is rare. I do not encourage use of drugs during the first trimester because there are unknown risks and the problems are usually self-limited.

There are patients who tolerate discomfort poorly, and they want something for help.

Mr. **Walgren**. On one of the things that strikes me in this area is that every pregnant woman does experience nausea—or by and large—and put a drug on the market and actively market it for relief of that symptom and one everyone is going to complain about and probably most people that have never been pregnant are apprehensive about and wonder what that experience is going to be—it seems to me there would be a tendency for overuse of that drug or use under circumstances that are not ultimately compelling.

My problem is I read the label on the drug and it is in such confusing language that any warning or true restriction of that drug to the ultimate case where you really would feel that the risk whatever it is may be justified because of the need of that patient—the warning is so diluted that I would think commonsense tells us people are taking this drug way beyond what you recommend, what FDA recommends, and even what the manufacturer recommends.

Do you have any suggestion?

Dr. **Ryan**. We are a drug-taking society. The taking of mood-altering drugs, for example, is extraordinarily high. I am not here to grandstand about abuses in the drug industry. I am talking just about pregnancy. We all know the first trimester is a high risk area. Later on in pregnancy the risks are less when known.

I would recommend that we avoid drug use unless all else fails. I think there are alternatives and a lot of what the patient does will depend upon the kind of care and support she gets from the health care system.

Mr. **Walgren**. You rely on FDA to represent that a drug is ineffective, do you not?

Dr. **Ryan**. Yes and no.

Mr. **Walgren**. There would be no point in prescribing a drug that was not effective.

Dr. **Ryan**. I think at the minimum I would say yes, but I do try and get students to go back and look at the original studies and see what was done to establish the efficacy of the drug, whether or not there were controls, whether they were blinded.

There was discussion earlier about whether the drug design was available to FDA. I would like the FDA Commissioner to respond to that. I can assure you that the drug design is a critical part of the drug approval process, and the FDA ordinarily controls the nature of the drug design.

I think you should pursue that. We do rely on FDA and their advisory committees to help us, but we also try to go back to the original literature as well.

Mr. **Gore**. Thank you.

A couple of more brief questions.

First, it is true, is it not, that you were chairman of the National Commission on Research.

Dr. **Ryan**. Protection of human subjects.

Mr. **Gore**. You all concluded that the mother should not be allowed to consent to participate in nontherapeutic research directed at the fetus after a decision to abort.

Dr. **Ryan**. Yes.

Mr. **Gore**. I agree with that decision, but the reason I make note of it in the record at this point is to highlight the fact that that decision does represent a barrier of sorts to the acquisition of more information in this particular area.

I think it is an appropriate decision and a barrier that should remain, but in discussing the absence of data we ought to realize that some of the absence of data is due to that ethical decision.

Dr. **Ryan**. May I also respond to that because I think that we received a lot of testimony about the need for research, involving aborted fetuses and the need for that kind of research is not great.

I don't think we should use the abortion issue, to cloud the whole question of appropriate research on pregnant women in which the concern is the future health and well-being of children.

Some people say because of informed consent you can't do research now, or if we had to apply our regulations today, we could not have done such and such research done in the past.

I find that argument specious and used as a rear guard attack on any regulations with respect to human research.

Mr. **Gore**. It was a close vote on the commission, was it not?

Dr. **Ryan**. That report was the first one the commission completed. We were under the gun from Congress because there was a moratorium on fetal research which stopped all kinds of research.

Scientists would not do any research in pregnancy at that particular time. At the end of 3 months, we rendered our report and suggested that the moratorium be lifted.

Mr. **Gore**. Mr. Shamansky?

Mr. **Shamansky**. Thank you, Mr. Chairman.

Dr. Brackbill, I was so taken—and I think the chairman responded the same way—with the commonsense aspect of your suggestion that there be two versions of obstetric medical information, one for the consumer and one for the professional.

Why in the world isn't there?

Dr. **Brackbill**. That is a question that ought better be directed I suppose toward the Commissioner of FDA and the head of DHHS. It is very possible to displease effective consumer information. U.S. Pharmacopia is starting to dispense information for patients that is in readable English, written at a 6th-grade level. They were shooting for 4th-grade level, but they ended up with 6th-grade. It is eminently understandable and clearly written. They are at present dealing with drugs frequently used in pregnancy.

Mr. **Shamansky**. Is there resistance coming from the drug companies to using the two versions?

Dr. **Brackbill**. I don't know how extensively U.S. Pharmacopia is distributed, particularly the dispensing information for patients. This is something that is a relatively new item in their production, and of course it is privately funded.

It is not due to any FDA efforts—as a matter of fact, they did have some resistance from FDA to their undertaking this task.

Mr. **Gore**. If I could be so bold as to advance an answer to my colleague's questions, I don't think there is any doubt whatsoever that the pharmaceutical industry has so strongly and violently opposed a greater effort to provide information directly to the consumer.

It is purely financial both with respect to the cost of printing the information and perhaps with respect to the concern that the greater availability of that information would lead to a dramatic reduction in the use of the products being manufactured so profitably today.

That is exactly what I believe. The import of your study, Dr. Brackbill, is that in fact pregnant mothers do not have the information to which they are entitled as citizens of this country.

Mr. **Shamansky**. Just the one question. Is there anything necessarily irreconcilable between the goals which Mrs. Haire is seeking and what you think is fair?

Dr. **Ryan**. Not at all, but I don't want to be misunderstood. I have not read the 15 or 20 recommendations she made in detail.

Mr. **Shamansky**. I am not talking about the recommendations. I am talking about the general thrust.

Dr. **Ryan**. With respect to the recommendations that Dr. Brackbill made, I am in complete agreement that patients ought to be informed. It ought to be a system of information that they can understand.

I don't know whether we have done enough research on the type of information that should be given to patients. They are beginning to look now at this. There was this concern about a package insert for estrogen use postmenopausally.

I think that we are better off, with more public information, I agree with Mrs. Haire. Physicians are better off, and drug companies are better off when more complete information is provided.

Mr. GORE. Thank you very much. Thanks to your patients, who have been inconvenienced by your appearance here today. Dr. Brackbill, thank you for your testimony and the excellent work you have done in this area. We appreciate it.

Mr. GORE. Our next panel consists of Dr. Phillip Goldstein, chairman of the Department of Obstetrics and Gynecology at Johns Hopkins University Medical School; Dr. Sanford Cohen, chairman of the Department of Pediatrics, Wayne State University; and Dr. Sumner Yaffe, professor of pediatrics and pharmacology at Childrens Hospital in Philadelphia.

If you would make your way to the witness table.

Welcome, gentlemen. We certainly appreciate your willingness to come here today and your patience throughout the morning. Without objection, your prepared statements will be put into the record, and we would like to begin the presentations with you, Dr. Goldstein.

Welcome, and please go ahead.

STATEMENTS OF DR. PHILLIP GOLDSTEIN, CHAIRMAN, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, JOHNS HOPKINS UNIVERSITY MEDICAL SCHOOL, BALTIMORE, MD.; DR. SANFORD COHEN, CHAIRMAN, DEPARTMENT OF PEDIATRICS, WAYNE STATE UNIVERSITY, DETROIT, MICH.; AND DR. SUMNER YAFFE, PROFESSOR OF PEDIATRICS AND PHARMACOLOGY, CHILDRENS' HOSPITAL, PHILADELPHIA, PA.

Dr. GOLDSTEIN. Thank you very much.

I will probably deviate from my prepared statement several times since it is in my nature to ramble. I am a simple country doctor from Baltimore, and we tend to do that.

I would like to indicate, though, that there was a question raised earlier about ultrasound in two or three issues, and as a high risk obstetrician, we do use ultrasound a lot.

I would like to call the committee's attention to a phenomenon that you are probably familiar with. If you are going to look at the outcome of ultrasound, you have to control that outcome based on the indications for the use.

Now, if you have people who are having abnormal bleeding or abnormal presentation, abnormal uterine growth early in pregnancy, and you subject that type of people to ultrasound, one of these questions I would you to ponder during the remainder of my presentation is how are you not going to offer ultrasound to half a group and say that the outcome in one group was better or worse than the outcome of the former group?

I am sure Dr. Slone will discuss that at greater detail.

Mr. Gore. Obviously you can't. It is the same kind of limitation that hampers the acquisition of data in other areas that this issue raises.

Dr. Goldstein. I did not want to leave the issue of ultrasound hanging as to there is something that is being perpetrated daily and the outcome of a patient with who requires ultrasound would result in an abnormal fetus. In fact, it might be exactly the opposite, but that is another story.

Mr. Gore. But a second-best study could be done. The best kind of study from a clinical point of view would be the one you described, which cannot be performed. A second-best study would be to follow up the outcomes of fetuses upon whom ultrasound was used and compare it to a control group that had not been subjected to ultrasound.

Dr. Goldstein. I smiled at your second-best study. Maybe we will talk about that in a second. Let me continue.

I also want to thank whoever designed the introduction because I feel like queen for a day. I am not chairman of Johns Hopkins. My boss would probably get very nervous.

I am obstetrician and gynecologist-in-chief at Sinai Hopsital in Baltimore. This is one of the largest, if not the largest obstetric service in the State. Dr King is the professor and chairman. I am salaried by the hospital, and I specialize in high-risk pregnancy, or maternal fetal medicine.

I am, therefore, in position to view the medical care of the pregnant women from both academic and private practitioner points of view.

The outcome of these pregnancies is a physically normal and healthy baby at least 90 percent of the time. The other 6 to 10 percent yield babies who have either congenital heart disease, cleft lip and/or palate or some other anomaly.

It took many years to define this four- to eight-fold increased risk in such situations because of the small number of such pregnancies each year and the poor reporting network that existed for so many years.

This stresses the need to maintain a good surveillance program for epidemiological research. However, now that this risk is known, what can a physician, what can a regulatory agency establish as a procedure to follow or a general policy for each young woman without epilepsy.

Some physicians suggest that all such women should be advised never to have children. Others suggest that medication should be stopped when pregnancy is planned, or occurs without planning, a very hazardous suggestion, not taken seriously by most physicians since a woman who needs the anticonvulsant therapy can be harmed and her pregnancy jeopardized if drugs are discontinued and seizures allowed to occur without greater frequency, while others—including me—suggest that women without epilepsy that requires treatment should not receive anticonvulsant therapy into their child-bearing years because of an old history of a seizure disorder and women who truly need treatment receive the treatment and encouragement that, while warning of the risks, stress the positive side of the available data; that is, more than 90 percent of the time the baby will be normal and in most cases where abnormalities occur, the abnormality is not life-threatening and can be repaired surgically.

This is medical practice, and it cannot be regulated effectively by an agency such as the FDA. Government could impact on this type of problem through stimuli that will improve all phases of medical education in this important area and through regulations that mandate intensive post-marketing scrutiny of the outcome of pregnancy when a new drug is introduced into clinical use for conditions such as epilepsy—and there are many others—for which reasonably good agents are already available and we know the risks these agents pose.

I will not expand upon the type of aberration that may lead to fetal growth retardation since time is short, but I would like to say a few words about the problem of early infancy functional problems, since these are truly pediatric issues and are probably far more frequent historically than the more dramatic teratological conditions we hear so much about.

These functional abnormalities may involve attention span, the ability to respond appropriately or to extinguish responses when appropriate after visual or auditory stimuli. They may involve sucking efficiency or the sleep-awake cycle. They may last only a few hours or a few months, but they are real, and their long-term implications are still not known.

The drugs that produce them are generally administered to deaden pain or to alter the state of consciousness and/or awareness and anxiety in the women during the course of labor.

The FDA may have a role in protecting infants from the as yet unknown consequences of the apparently temporary alterations in function mentioned above. The agency might attempt to develop a statement for the labeling that goes with any drug that affects the central nervous system or behavior which points out that all such drugs should be used with discretion during labor since they have the potential to depress the newborn infant's functional capabilities for a variable period of time after birth, as well as the woman's, when administered prior to the infant's birth.

Finally, let me state that the pregnant woman is considered to be a member of a special group whenever there is discussion concerning the ethics of human experimentation. Other special groups include minor children and institutionalized individuals, whether retarded persons, prisoners, or residents of a psychiatric facility.

Pregnant women are special in the main since the risks to the fetus of investigation on the woman may not be known and, even if known, there is some question of the ethical and legal status of her consent for research that will affect her fetus.

One major advance that I would like to encourage is the development of a mechanism whereby as much information as possible can be gleaned for our future knowledge from careful studies of women, their fetuses, while still in utero, and their infants after birth, when there is a true medical indication for the introduction of a new drug's use, or the use of an older, poorly studied drug, during the pregnancy.

Such studies will be in a much clearer ethical and legal position but will require the availability of skilled individuals in a number of locations to take advantage of the clinical situations as they arise.

The subject of drugs and pregnancy is extremely complex. Very simply put, I see the process as being one in which all parties who take care of pregnant women agree that there are likely to be "victims," the children. But, who are the "criminals"? The mothers who inadvertently take the drugs? The FDA for not having the wherewithal to properly test drugs, especially on humans? The physicians who prescribe drugs believing that the drugs are useful? Or, the drug company who develops a drug which they feel will impact on health in a positive sense? There is no question that some drugs are likely to affect the fetus. On the other hand, there is no question that some drugs are extremely necessary in the care of pregnant women and the risk versus the benefit of these drugs must be weighed.

Consider the dilemma of the delivery of a premature child. Although we know of several factors that predispose a pregnant woman to give birth prematurely, the most common situation is one in which the pregnant woman goes into labor prematurely without apparent cause. The major cause of mortality in newborn infants is prematurity, because the premature is born with immaturely formed organ systems such as the brain, the lungs, the kidney, and the liver. Such children are extremely fragile and are at risk for birth injuries and complications of care. Therefore, the prevention of such labor is one of medicine's highest priorities. In an effort to prevent premature birth, drugs have been used for several decades to inhibit uterine contractors.

One class of drugs is based on a family of hormones, one member of which you may recognize by the name "adrenalin." Adrenalin itself is not used as a labor inhibiting agent. Such hormones, when altered by skillful chemists, can be changed so that some of their troublesome side effects are reduced, and their more desirable effects emphasized. One such desirable effect is the inhibition of labor. Since these agents affect many organs in the body, and since they travel from the mother through the placenta into the baby, the need to evaluate the long-term side effects of such agents is of critical importance. To date, despite the fact that such drugs are being used, some with FDA approval, little comprehensive long-term followup with appropriate controls is ongoing in the children who receive the drugs while their mother is in labor, whether the labor stops or not.

Obviously this drug fails in a reasonable number of cases, and as a result, the child is born with the drug physically measurable onboard. Here we have a situation in which literally millions of doses of these drugs are reaching the most fragile of our newborns, the premature, without a scintilla of evidence to support the concept that in 21 years behavioral change will not occur in these children, changes which may be contrary to normal society. Alternatively, should such drugs prove to be extremely effective and hundreds of premature infants are saved but 1 in every 100 is damaged as a direct result of the drug, what do we do then? Do we focus on the 99 who might not be alive except for the drug or on the one, the casualty, the victim.

This is not mere conjecture on my part. I am sure you are familiar with the recent medical story in which diethylstilbestrol, or DES, was given to pregnant women in the mistaken belief that the pregnancy would be helped and supported hormonally by the drug. The female offspring of the mothers who received DES seem to be at risk for the development of an unusual form of cancer of the female reproductive system. This cancer, of course, is not going to be present as soon as the child is born, but may appear at an unknown period of time far along in the young woman's lifetime.

This then illustrates that today's drugs may not cause disease for literally years after the baby's birth. But the physicians who prescribed the drug certainly never intended to damage the children, as some media coverage make the situation seem. For another extreme example, one can simply look at the apparently most innocuous agent, yet most vital agent, used in treating premature infants. The agent is oxygen. Certainly, nobody would deny that oxygen is a vital component to medical care for individuals having respiratory distress. Unfortunately, as many as 10,000 children were blinded as a result of the use of oxygen.

Dr. William Silverman has used this example to try to impress on the rest of his medical colleagues that only by controlled clinical trials can we evaluate any agent. He has also stressed that blindness of a similar nature occurs even without high oxygen, which child would have been blinded anyhow. He has almost despaired of being able to convince the American public and, indeed, his medical colleagues, that just because we feel good about a therapy does not mean that the therapy is, in fact, a good one. A great professor has stated, "I can give all of my patients a drug; I can't give half of my patients the drug."

The control of which I speak probably cannot come from the Federal Government through FDA. The control must come from clinical trials conducted in environments in which scientific inquiry can be allowed to flourish. Consumers should have input into the process since the system exists to benefit, not hurt, them. In such an environment, multiple drugs which inhibit labor, for instance, might be compared on a national basis. The epidemiologists and bioethicists have more to say on this subject, I am sure.

I would like to address a few questions about the role of the FDA and drugs in pregnancy. I can understand and appreciate the concern that those of us who use drugs in pregnancy are never completely sure of subtle or not so subtle side effects which may affect the fetus. I also understand that the FDA is the watchdog of the American people, whose job it is to protect citizens from untoward events relative to drugs. Realistically, however, how is it possible to monitor all drugs used and all effects identified? Such a surveillance is clearly impossible and would stretch our resources far beyond their capability to expand.

I mentioned to Mrs. Haire that if the aspiration for oversight by FDA were to be fulfilled, it would make the Pentagon look like an anthill. Ultimately, we will always be dependent on the appropriate controls of science, physician compliance, and patient education.

If I may, I would like to indicate to you some of the problems with which both the practicing obstetrician and the academic obstetrician must deal in such drug trials. First of all, people must be randomized as to those who receive and those who don't receive drugs. The howls of indignation which may result when the public perceives that a drug is being withheld from one group is very evident in the recent laetrile controversy. For instance, Mrs. Haire's well-meaning criticism of drug effects as a consumer advocate, could easily be matched by women who received labor pain relief and thank God for it.

What are the physiologic results of unrelieved discomfort in the fetus? Psychological imbalance, emotional imbalance. When a woman is terrified, there is no question that there may be—there is a distinct possibility that the hormonal response to fear may have an adverse effect on uterine blood flow and on into the intrauterine passage.

Mr. **Gore**. I am compelled to interrupt at that point, if I might briefly. The very subtle and difficult ethical issues which are raised by exposing the fetus as well as the mother to drugs which carry risk with them I think in the past have been short circuited by an assumption on the part of too many that the fetus is also put at risk by pain experienced by the mother. The amount of evidence to support that link is how much? Is there any?

Dr. **Goldstein**. Yes, there is. Mr. Shamansky was addressing that question to Mr. Ryan in a little bit different way which is why the medical profession has not responded in a certain way to known events. You may be surprised to hear that there may be some class strata in academic medicine and there is no question that a fine amount of research on the effect of catcalmine release, which is a fear-producing hormone, in fact, may have significant effect on fetus and labor. That is in the subhuman primate, and as a consequence, it is subject to critical review.

Similar data is not available in the human, but there is a decent body of information about catcalmine release in the subhuman primate.

Mr. **Gore**. Please proceed.

Dr. **Goldstein**. Another problem obstetrically is the precise definition of premature labor. Uterine contraction or labor pains commonly recede spontaneously, and not all women who have uterine contractions will continue in premature labor. Second, what we know about premature labor is that the more advanced in labor the patient becomes as evidenced by changes in her uterus, the less likely we are to be able to stop that process.

So the most important controlled clinical trial that we could develop would, by necessity, involve a large number of women, whom we know by experience would never continue to go on to deliver a premature child. Yet, we would have to include them in order to guarantee that we would know which drugs would be effective in stopping the rest who might have delivered.

Needless to say, the numbers of women which would have to be recruited would be tremendous since the large percentage of each group that was used as the control group, meaning receiving no drugs, would probably stop spontaneously. Another problem with such a study would be that the term of the followup of the infants should be dozens of years. While awaiting the outcome of such a trial, we would be denying women currently in premature labor the use of an agent which, to the best of our information, seems to be very effective in stopping labor.

Another problem is the woman who would choose not to be a part of such a study, which of course would be their right. But that would mean that the study groups were, in fact, biased by selection. And what if in 21 or 30 years, the offspring who are born, who had the drug during the premature period, and were successfully kept in utero, manifested some behavioral change or an abnormality which seemed to be related to the drug? Would the manufacturers or the physician who used the drug and possibly saved the child's life be subject to a medical malpractice suit?

I was interested in Mr. Bingham's presentation because in the 15th or 16th paragraph which he submitted from the newspaper—I believe it was called the Co-Op News—it mentioned that the individual who had the brain-damaged child had a suit against the institution in which the alleged offense had occurred. The institution offered the plaintiff an award, an amount of money. However, the plaintiff turned down the award, and the trial was brought to suit and the defendant was found not guilty. So a jury of peers in one of the indexed cases helping to promote this topic found the defendant in the case not guilty.

Mr. GORE. I am not sure what you mean. Do you mean the question: Would the manufacturers or the physician who used the drug and possibly saved the child's life be subject to a medical malpractice suit? I know you are not advancing that as a reason for not doing the study.

Dr. GOLDSTEIN. No, I think it is a question that needs to be answered and some clear direction given.

Mr. GORE. It comes at the end of a list of difficulties that would be encountered in doing the study. Do you intend that to be another difficulty?

Dr. GOLDSTEIN. Absolutely. If you are going to recruit private physicians, they need some assurances that in conducting a trial for the good of mankind they are not swept up in some practice which, in fact, is going to seriously impair their ability——

Mr. GORE. So you do mean that?

Dr. GOLDSTEIN. Sure.

Mr. GORE. I understand what you are getting at. Please go ahead.

Dr. GOLDSTEIN. While we are focusing on the premature as a fragile recipient of drugs, the apparent effects of alcohol and smoking in causing premature and low birth weight babies far outweighs the consequences of other drug use. In fact, it is very likely that smoking, alcohol, and poor nutrition cause as much mischief in human development as all other drugs put together. Should good nutrition be classified as a "drug" by this committee? If this inquiry has as its goal the overall health of the American people, decent prenatal nutrition must be the cornerstone.

Obviously the environment in which drugs are given depends on the state of the recipient ingesting the drug. A poorly nourished person will have a different drug interaction with nutrition, for instance, than a well-nourished person. For instance, in a good, well-balanced diet, prior to and during pregnancy, iron tablet supplementation might not even be necessary. Yet, iron provision is a common drug used in pregnancy.

Lastly, the media are not an appropriate forum for scientific inquiry and debate. The New England Journal of Medicine has a policy that any finding, drug related or not, which has been released to the press before a board of editorial policy has reviewed the adequacy of the data and the adequacy of the conclusions will not be published on its pages. One cannot have an emotional and strident debate which polarizes groups, consumers versus providers, and expect to see improvement in the way we care for women and children. Only by the use of calm, scientific, objective inquiry are we going to be able to identify whether we are doing better or worse than we might have done without the technology currently available.

I want to thank you for allowing me to be with you today, and I would like to try to answer any questions which my presentation might have generated.

Mr. Gore. Your last paragraph should not be interpreted, should it, as a recommendation to withhold data from consumers and allow it to appear only in scientific journals?

Dr. Goldstein. No. The fact that Mrs. Haire had something to do with me being here, I think, lends credibility to the fact I don't think withholding information is in any way going to improve the health of our people. I think you should never withhold information, but the information has to be presented in an objective form.

All of us can cite the sensational beings extracted out of a paper which in fact may have been conjecture on the part of the author in the discussion part of a paper which may or may not apply to the data which the author has generated.

Mr. Gore. Let me note in passing I certainly agree with you about the nutrition, and smoking, and alcohol. No question about it.

Mr. Gore. Thank you. Now, Dr. Cohen.

Dr. Cohen. Thank you, Mr. Chairman.

In addition to the title which is listed for me as chairman of the Department of Pediatrics at Wayne State University, I would like to identify myself with some of the other things I do. I am also pediatrician-in-chief at the Children's Hospital of Michigan in Detroit. I am also an associate member of the Department of Pharmacology at Wayne State and an adjunct lecturer in the School of Public Health at the University of Michigan.

I have been a student of some of the issues being discussed this morning for nearly 20 years. I have taken the liberty of distributing to staff copies of two papers on the subject of ethics of drug research in children.

I should like to point out at the outset that while not an apologist for the Food and Drug Administration, I have been quoted as an admirer of the way the agency acquits itself so well, in general, in the face of an impossible charge. It has perhaps the most numerous and disparate responsibilities of any comparable governmental regulatory body in the world.

Furthermore, in the area of protection of the fetus and newly born the FDA has mandated responsibilities that far out strip any human agency's ability to fully comprehend, let alone fulfill. This is due to the biology of development and because of the value of the possible embryopathic and fetopathic effects of foreign compounds introduced during a woman's pregnancy.

There are four main types of pathologic effects that may be ascribed to drugs taken during pregnancy. These are (1) severe abnormalities of embryonic, fetal, or maternal physiology which lead to intrauterine death and/or spontaneous abortion (or miscarriage); (2) structural defects in the developing fetus (teratogenesis); (3) growth retardation during intrauterine life; and (4) functional defects, which frequently manifest themselves during the periods of early infancy that follow birth. It must be recognized that human pregnancy and fetal development is unique in biology in more than its end product: there is no other species which has the same combination of type of placentation, duration of normal festation, exposure to changing environmental and emotional conditions, variation in dietary intake and rest-exercise cycles, and a host of other characteristics of the human. To be sure, many specific characteristics are mimicked by other species or can be produced in laboratories, but as in other issues involving a question of variations from a broad range of what we refer to as normal situations, only the universe of human gestations and births are the proper control for births which occur under certain unusual conditions, such as in the presence of drugs.

While there is no certainty, it is likely that a drug which disturbs physiology enough to cause fetal death in man will also cause death, or at least obvious deviations from normal in laboratory animal species. Thus, initial screening of drugs in the laboratory should reveal which ones must be excluded from use by women of childbearing age who may become pregnant during the course of therapy. Of course it must be understood that, as is always the case, this general statement should be modified in specific clinical situations. For example, if the drug in question is the only one available to treat a seriously ill woman, it might be indicated to prescribe it with the caution that she take steps to avoid pregnancy, and worry about the product of a pregnancy that occurs despite the warning afterwards.

Furthermore, should a drug slip through such screening practices, its effects upon fetal development should become known very shortly after it is introduced into clinical use, if there is an appropriate method available to accumulate data on miscarriages in women who have taken the drug.

Structural defects are produced during the period when structures are being formed, or during the preceding periods when early embryonic cells are being organized to form the structures. The period of organogenesis, excepting CNS, in man is completed before the 60th day of gestation, when the two separate precursors of the palate fuse in the midline on approximately the 57th day after fertilization. Thus, in the human all physical-structural defects are produced during a period when many women are unaware of their pregnant state and many are produced, or predetermined, during a period when no woman can be aware of her pregnancy.

The incidence of physical anomalies in our population is approximately 30 per 1,000 live births or 3 to 5 percent. Fewer than half of these are significant in the sense that they are a threat to the infant's normal growth and development or require significant surgical intervention. Close to 70 percent of these anomalies cannot be traced to a provable cause at the present time. Only about 2 percent are regarded as known to be associated with specific drug use early in the pregnancy. Intensive epidemiological studies over long periods of time are essential if we are to define the associations of some of the other anomalies with specific drug entities. Even after the association is known, it will almost certainly be one of increased risk rather than a causative association in a specific case. Let me use an example to explain the meaning of this: Approximately 3 live births per 1,000 occur in epileptic women, almost all of whom have received anticonvulsant drug therapy throughout their pregnancy and, indeed, for some time prior to conception.

The outcome of these pregnancies is a physically normal and healthy baby at least 90 percent of the time. The other 6 to 10 percent yield babies who have either congenital heart disease, cleft lip and/or palate, or some other anomaly. It took many years to define this fourfold to eightfold increased risk in such situations because of the small number of such pregnancies each year and the poor reporting network that existed for so many years. This stresses the need to maintain a good surveillance program for epidemiological research. However, now that this risk is known, what can a physician, what can a regulatory agency establish as a procedure to follow or a general policy for young women with epilepsy? Some physicians suggest that all such women should be advised never to have children. Others suggest that medication should be stopped when pregnancy is planned or occurs without planning—a very hazardous suggestion not taken seriously by most physicians, since a women who needs the anticonvulsant therapy can be harmed and her pregnancy jeopardized if drugs are discontinued and seizures allowed to occur with greater frequency—while others—including me—suggest that women without epilepsy that requires treatment should not receive anticonvulsant therapy into their childbearing years because of an old history of a seizure disorder, and women who truly need treatment receive the treatment and encouragement that, while warning of the risks, stresses the positive side of the available data, that is, more than 90 percent of the time the baby will be normal and in most cases where abnormalities occur the abnormality is not life-threatening and can be repaired surgically. This is medical practice and it cannot be regulated effectively by an agency such as the FDA. Government could impact on this type of problem through stimuli that will improve all phases of medical education in this important area and through regulations that mandate intensive postmarketing scrutiny of the outcome of pregnancy when a new drug is introduced into clinical use for conditions such as epilepsy—and there are many others—for which reasonably good agents are already available and we know the risks these agents pose.

I will not expand upon the type of aberration that may lead to fetal growth retardation, since time is short, but I would like to say a few words about the problem of early infancy functional problems, since these are truly pediatric issues and are probably far more frequent historically than the teratological conditions we hear so much about. These functional abnormalities may involve:

attention span, the ability to respond appropriately or to extinguish responses when appropriate after visual or auditory stimuli. They may involve sucking efficiency or the sleep-awake cycle. They may last only a few hours or a few months, but they are real and their long-term implications are still not known. The drugs that produce them are generally administered to deaden pain or to alter the state of consciousness and/or awareness and anxiety of the woman during the course of labor. The FDA may have a role in protecting infants from the as yet unknown consequences of the alterations in function mentioned. The Agency might attempt to develop a statement for the labeling that goes with any drug that affects the central nervous system or behavior, which points out that all such drugs should be used with discretion during labor since they have the potential to depress the infant's functional capabilities for a variable period of time after birth, as well as the woman's when administered prior to the infant's birth.

Finally, let me state that the pregnant woman is considered to be a member of a special group whenever there is a discussion concerning the ethics of human experimentation. Other special groups include minor children and institutionalized individuals whether retarded persons, prisoners, or residents of a psychiatric facility. Pregnant women are special in the main since the risks to the fetus of investigations on the woman may not be known, and, even if known, there is some question of the ethical and the legal status of her consent for research that will affect her fetus. One major advance that I would like to encourage is the development of a mechanism whereby as much information as possible can be gleaned for our future knowledge from careful studies of women, their fetuses while still in utero, and their infants after birth when there is a true medical indication for the introduction of a new drug's use—or the use of an older, poorly studied drug—during the pregnancy. Such studies will be in a much clearer ethical and legal position but will require the availability of skilled individuals in a number of locations to take advantage of the clinical situations as they arise.

Thank you for the opportunity to address you this morning. I look forward to the discussion that will follow these presentations.

Mr. GORE. Thank you. Now Dr. Yaffe.

Dr. YAFFE. Thank you.

I would like to thank you for the opportunity to appear as a witness. The subject under discussion has been of concern to me—since I am older than Dr. Cohen—for more than 20 years as contrasted to his 15.

As the two previous speakers, I also would like to correct the academic affiliation listed on the witness list. My academic affiliation is with the University of Pennsylvania, although I am located physically as director of clinical pharmacology at the Children's Hospital of Philadelphia.

Mr. GORE. We will go through the record and make the appropriate corrections so that people who are in these positions are not concerned.

Dr. YAFFE. I have submitted for the record two documents, and I believe you have them. What I should like to do is, primarily to expedite the discussion in light of the purpose of these hearings and, second, because I believe that undernutrition may be of great harm to those of us who are not pregnant, male and female, to end my testimony quickly, and thus enable us to have lunch.

What I would like to do at the beginning is to briefly respond to the nine questions that were posed several weeks, ago I think there has been sufficient discussion throughout the morning on several issues, which I would like to raise again and offer my own opinion, perhaps providing a little different tack to the answers that were given.

The first question is what drugs which are currently on the market present a significant risk to the unborn child when used during pregnancy. That is a difficult question to answer, as you have heard this morning, since the risk is difficult to assess.

There are few relevant animal models, and clinical evaluation of safety is in many instances ethically as well as scientifically impossible to undertake. As a consequence—and this also answers question 2—the overwhelming majority of drugs have a disclaimer concerning usage during pregnancy.

Therefore, since the risks are unknown, it is impossible to inform physicians about specific adverse effects. On the other hand, as has been mentioned by other witnesses, it is possible to educate physicians concerning the potential hazards which result from using drugs with unkown risks.

In this case, the physician must weigh the benefit versus the risk, as he must do, and I would like to emphasize this point, when prescribing drugs for any patient, whether it be male or female.

The physician must always go through this benefit versus risk analysis. If there is no benefit, then there is no question to be asked, you just don't use the drug.

I also believe, as Mr. Ryan stated this morning, that there has been a considerable improvement in attitude and many of the younger obstetricians are aware of what we have been talking about this morning concerning the usage of drugs that have not been evaluated, unknown risk drugs.

I think there has been a decrease in the usage of nondiscretionary drugs. I will get back to that issue later. It is impossible to rely upon animal toxicology to predict adverse effects upon the human fetus.

It is, in my opinion, important that methodology be improved by developing relevant animal models. This will occur only with the elucidation of the basic mechanisms responsible for the production of adverse effect.

So, what I am saying is that we need more research into the fundamentals of how a drug can produce a given effect during pregnancy. In my opinion, methodology is improving as our understanding of mechanisms increases.

Evaluation of the effects of drugs upon the fetus when administered to the pregnant woman can be undertaken, as several previous witnesses have indicated, with the use of epidemiologic techniques. These investigations can be planned prospectively for those uses of the drug where the benefits are great.

In this case, extensive followup examination is needed. Epidemiologic information plays an important role in making decisions about drug prescribing. This is in answer to question No. 7. Of course, other information, such as drug disposition and action, are also important.

As we are all aware in answer to question 8, the Food and Drug Administration adheres to the Kefauver amendments of 1962 in the approval of any new drug. Thus, a disclaimer is generally incorporated into the label to indicate that an evaluation has not been conducted during pregnancy.

In my opinion, more concern could be focused by the FDA in support of epidemiologic studies to monitor previously approved drugs. Postmarketing surveillance could be undertaken with respect to drugs administered to pregnant women.

I would like to remind the subcommittee that in 1974 I had the privilege of chairing the Committee on Drugs of the American Academy of Pediatrics. At that time we had a contract from the Food and Drug Administration to develop guidelines for the evaluation of drugs to be used in pregnant women and in children.

We recommended in our final report, which was submitted 7 years ago to the Commissioner, that postmarketing surveillance for drugs be emphasized as a means of obtaining safety data.

Finally, question 9, the Food and Drug Administration can encourage the pharmaceutical industry to undertake studies prior to marketing for those drugs which will have major usage in the pregnant woman.

This was recently undertaken, as several other witnesses have mentioned, with the recently approved and marketed drug Ritodrine, an inhibitor of uterine contractions. I don't think there was any trouble in getting the requisite studies done when there was a drug which had a specific indication for usage in pregnant women.

It has been mentioned before, there are very few drugs that have actually been approved for use in that state. As far as I can tell from my cursory review, there are only two. Ritodrine is one, and the other is Bendectin.

I don't think that many other drugs, as the first witness (Mrs. Haire) has stated, have been approved for pregnancy. I would like to add a plea for the need to expand our concepts of drug effects beyond anatomical malformations to effects upon fetal functions.

If we accept the broader approach, I recognize that difficulties of incriminating environmental agents are increased manyfold. In addition, effects may be subtle, unexpected and often delayed, compounding the problem of ascertainment, even further.

I might add that a subject which is of great concern to me, which has not been discussed at all today, but which clearly impacts upon the outcome of pregnancy, is the effect of drugs upon the father, who is obviously making a 50-percent contribution to the outcome of pregnancy.

I don't know whether the subcommittee is aware of the fact that there are published reports, some of them actually going back to 1860, of the adverse effects of drugs and environmental agents administered to men before fertilization, before the pregnancy developed, upon the results of pregnancy.

Clearly an understanding of the mechanisms underlying the production of adverse effects from drugs and chemicals is needed so that animal models can be developed which are specific and directly applicable to the reliable assessment of safety.

Long-term effects of drugs in particular will not be elucidated in the human because the very nature of the period of observation is beyond the possible interests or ability or even lifespan of most clinical investigators.

Animals with a much shortened life cycle are clearly of value, but the selection of the appropriate animal species must be based on a scientific understanding of the mechanism involved, not bureaucratic regulation that two animal species be employed in pretesting evaluation.

Finally, there is a need for human data since we are now in the era of fetal diagnosis, an area that has not been mentioned this morning, and fetal therapeutics is an obvious and sectarial consequence of fetal diagnosis.

In other words, there is no point in making a diagnosis unless you can do something about it. Data must be developed to make the administration of drugs to the fetus for the treatment of fetal disease as rational and as therapeutic as in the adult organism. This requires study and knowledge disposition and action within the fetus in the placental unit.

Before closing, I would like to respond to several comments that previous witnesses have made and several comments which members of the subcommittee have made.

There was, for example, considerable discussion by Mr. Shamansky about the liability of government. I have just come back from Japan this past week and participated in some committee deliberations with what is the equivalent of the Food and Drug Administration.

It was made aware to me that the Government of Japan does share 50-percent responsibility for damages, financial responsibility, in case these occur. So that they have an even greater drug lag than some people think we have in this country because they are extremly cautious about approval of new drugs.

I support, as others, the need for a patient package insert. I would wonder how useful this will be, however, because studies that have been conducted indicate that perhaps 40 percent of prescriptions are never filled by the patient. This means, if that trend continues, that at least 40 percent of the patients will never get the package insert because they wouldn't get the drug prescription filled.

Many women don't know when they are pregnant, as has been mentioned by others, and it is difficult to know when you query them as to whether or not they have been taking drugs.

I would like to cite a study that was done with aspirin. Aspirin is readily used during pregnancy. There is no question about that. It is used when you are not pregnant as well.

A few years ago a study was conducted at the University of Alabama in which a large number of women were asked whether they had taken aspirin on the day or two before delivery, so it was a very focused period of time. They were asked after they had delivered, and they all said no.

At the same time, these investigators had obtained a sample of the cord blood which, as you know in the routine practice of obstetrics, is always taken from the infant's umbilical cord.

They measured aspirin, and in a large percentage of women aspirin was present. There is no way it could have gotten there except by (in cord blood) being taken by the mother in the day or two prior to delivery.

Then they rephrased the question and began to ask about all the brand names of products which contain aspirin, and the answer was yes. I mention this as an example of the difficulties that we have in obtaining information about drug usage during pregnancy.

The question was raised, in commenting on Dr. Ryan's testimony about the statement he made about drug usage during pregnancy increasing. There is no question, I think, in the studies that have been published that this is so.

However, as Dr. Ryan indicated, I would also agree that the drugs that have been prescribed or taken by pregnant women, over-the-counter drugs, are discretionary drugs. Most physicians, in my opinion, are aware of some of the side effects, and prescribing of these drugs is in general decreasing, especially with younger physicians. So that I think educational messages have had some benefit and positive effects are occurring.

I would like to end by thanking you for the opportunity to be present. I think it is a most important area for discussion.

Mr. Gore. Thank you, and thank you all. Everything I have heard from the three of you appears to argue in favor of giving patients more information.

Dr. Yaffe. May I interrupt? You know I would never prescribe a drug to anyone—I have been discussing this this morning with Dr. Cohen—for any patient, pregnant, nonpregnant, male, female, infant, child, without going over the benefits of the drug, what the drug is for, what the side effects are.

One of the problems, of course, has to do with how much disclosure is involved. That is a matter of physician judgment.

Mr. Gore. What do you do with your patients when the FDA tells you that we don't know what the effects on the fetus are?

Dr. Yaffe. I would expand that, if I may, because, as you are aware, 78 percent or more of drugs used in pediatric patients after they are born have no information. So, we have this dilemma that always faces us in pediatrics. You have to tell them that we don't know whether it is safe, but if you have hypertension, as Dr. Ryan mentioned, and you are pregnant—I would have no hesitation in saying, you have hypertension, we know that this can be harmful to you and to your fetus.

Here is a drug that works, and even though the risks are unknown, I think it is important that you take it. Of course, the mother has an opportunity to say no, but I doubt that she would.

I might add that I always mention the father as another party in this decisionmaking process for the fetus.

Mr. Gore. Mr. Shamansky?

Mr. Shamansky. Dr. Yaffe, I want to go to something you mentioned in your testimony and that you just alluded to again. Am I safe in inferring from your testimony that you think the judgment should be up to the doctor as to what he discloses to the patient?

Dr. Yaffe. Well, the answer to the question is yes, but I would like to qualify that and explain what I mean.

Mr. Shamansky. That is tough to qualify, but go ahead.

Dr. **Yaffe**. I think there is a time when the anxiety associated with rare side effects that might occur might be productive of more harm in disclosure to the patient.

I think with common side effects, there is an obligation on the part of the physician to discuss these with the patient and to go over the whole benefit versus risk decision as to whether or not to take it.

In my personal opinion, we should allow the patients to participate in the decision, pregnant or not.

Mr. **Shamansky**. Dr. Cohen, would you like to comment?

Dr. **Cohen**. I am an example of a person that one of your distinguished predecessors in the Congress wanted; that is, I am an example of why the statement was made by a distinguished predecessor; that is, he wished there were such things as one-handed scientists because on all questions such as this you get, "Well, on the one hand this, and on the other hand that."

Mr. **Shamansky**. That is a point of lawyers, too.

Dr. **Cohen**. I have to tell you that I am emotionally committed to the concept of revealing all information in a relatively sterile, nonopinionated way and allowing people to have their choice.

But I am also aware, as a physician of the fact, that individuals, be they physicians, lay people or whomever, will have great difficulty in deciding upon the importance of the information when they are confronted with all of this information in a situation which therapy is obviously potentially indicated. Otherwise, it would not be brought to their attention.

There is one study in the literature that I believe needs to be brought out at this time, and that is one in which a group of educated, scientifically tuned-in young people, students in science and in medical school, laboratory technicians, et cetera, were given a series of statements concerning a pain killer.

The story was, we are experimenting with a pain killer and this pain killer has the following effects—it may cause the white cells in your blood to malfunction, it may cause intestinal bleeding, people have died from it, et cetera, et cetera, et cetera. If you have a headache, would you participate in this study by taking this pill? All of these people refused. Of course, the drug is aspirin.

The point is that one must use some discretion, someone or some agency must use some discretion in determining the information and how it is supplied to individuals.

So, on the one hand, Mr. Shamansky, yes, and on the other hand, I am afraid the answer may be no.

Mr. **Shamansky**. Not as a legislator, but as a lawyer constantly facing this situation, I understand the business of gray, I understand we use the word "reasonable" all the time. The thing I find startling here is not that the medical profession is trying to be reasonable in these things, but they are not doing it at all, apparently.

Dr. **Cohen**. I heard that comment of yours earlier, and I think Dr. Yaffe has already answered that to some extent when he pointed out that 7 years ago he chaired a committee made up of physicians put together by the American Academy of Pediatrics, a professional body of physicians, with the express desire to impact upon this area, and that that committee stirred the water up pretty good by making certain kinds of suggestions.

Now, what is the obligation of the professional bodies or individuals once they have taken that step and submitted the report and they have actually talked with people about the report?

I would suggest to you that since that report there have been a number of changes in operational policies and activities at the Food and Drug Administration which have moved in the direction of improving things.

I would submit, Mr. Shamansky, that the profession has had a hand in that, maybe not as much or maybe not as far as you or I would like to see it move, but there has been a hand. I was on that committee.

Mr. **Shamansky**. Are you implying that this is an unnecessary exercise, that things are hunky-dory and everything is going along super?

Dr. **Cohen**. Not at all. I am sure that no one on the subcommittee, or none of my colleagues with whom I have worked over the years, could mistake my action or statements to mean that.

I might say one innovative kind of thinking activity that has gone on in the recent past and which I believe the FDA is currently engaged in reviewing is the issue as follows: Given that a larger percentage of drugs are not approved for specific use in certain age groups of pediatric patients, and given furthermore that there needs to be available drugs for the treatment of patients in the various age groups and the condition of pregnancy, might it not be reasonable to have a panel of experts select one or maybe two chemical entities from the various classes of drugs, from each of the various classes of drugs, rather than all drugs in a class.

For instance, antibiotics, that is a class of drugs. There are some that are good against certain kinds of bacteria and some good against other bacteria. Let's take antibiotics effective against one type of bacteria and call that a specific class.

There may be 10 entities that are effective and perhaps none have been tested in the way we are referring to today. Wouldn't it be reasonable to select one or two of those entities without considering brand or manufacture and take improved drugs and try to get the studies done in one or two to get mechanisms available?

Mr. **Shamansky**. I think it is imminently reasonable, but I am appalled that it takes Doris Haire to keep raising the question for your profession.

Dr. **Cohen**. I would not get into an argument with you about that because Doris and I happen to be on the same side of every question.

Mr. **Shamansky**. Do either of you see anything you seriously disapprove of with Doris' approach under the way she is taking that?

Dr. **Cohen**. I am opposed to many of her approaches but I am not opposed to what she is seeking. There are specific things she has suggested because I believe she has been poorly advised.

Mr. **Shamansky**. I am obviously prejudiced, but she is an eminently sensible woman. If I may, Doctor, I would like to pursue this matter with Dr. Goldstein, just a little country physician or something like that from Johns Hopkins. Since the pages of your prepared statement are not numbered, it is about second from the back, you say,

> While we are focusing on the premature as a fragile recipient of drugs, the apparent effects of alcohol and smoking in causing premature and low birth weight babies far outweigh the consequences of other drug use that are known.

It is interesting to me that you threw in "that are known". It is not in your prepared text? But isn't that the problem, we don't know?

Dr. **Goldstein**. That is not the specific problem, but I felt it was commensurate with what I considered to be, without flattering anybody, a reasonably enlightened discussion this morning.

I don't feel as though I am threatened by saying I don't know something because anybody who knows me knows that I don't.

Mr. **Shamansky**. Do you want to be excused now as a witness after that disclaimer?

Dr. **Goldstein**. No. First of all, I would like to respond in just one sentence because Dr. Cohen has, I think, covered the subject very eloquently, at least as far as informed consent and total information dispersal.

This hearing, which is a product of governmental process, has an assumption at its base—and I don't want to get into an argument—that all people are created equal, and they are not. It is not an intelligence phenomenon about which I am speaking, but it is a level of education and a level of anxiety.

For instance, if we take the example of cancer chemotherapy discussion or if we take the more perhaps dramatic example of cancer radiotherapy discussion, many families and many individuals, when asked whether they want to know what the side effects may or may not be, or even whether they want the loved one to know whether they have the disease, will commonly try to protect their loved one by saying, I do not want that individual to know they have a malignancy. I don't want to know whether their hair will fall out or their white cells will malfunction or whether they will be more susceptible to infection.

To some of those patients, although it is contrary to my intellectual bent, it seems to make sense that you have to individualize patients. In the main, there is no question that we all agree that most complete information to the extent of our ability is in the best interests of our society. There are going to be exceptions, and I think that is the area that we all are bidding in a little bit.

As far as the fragile recipient of drugs is concerned, if, as I alluded to earlier, one discusses controls, meaning the control group in a population, if you give me or if one were to give us the axiom that the premature is the most fragile potential recipient of drugs, one legitimate conclusion would be to try the drug, a labor-inhibiting act, in term infants to determine whether this less fragile recipient might, in fact, be done some harm.

That drug and that test in a controlled way has not been done. Now we are willing to give this drug to premature infants without truly defining in any way who that premature infant is. Yet, we are unwilling to give the drug to children who are far more likely capable of accepting the drug based on, using your tenet, reasonable medical certainty.

Mr. **Shamansky**. I think that is a marvelous question. What kind of an answer do you have for it?

Dr. **Goldstein**. My research proposal was turned down by a university with which I am no longer affiliated.

Mr. **Shamansky**. Doctor, you say another problem with such a study would be that the term of followup from such a study would be dozens of years. My question obviously is, What do we do in the meantime?

Dr. **Goldstein**. I don't really know.

Mr. **Shamansky**. I think that is a little bit of a cop out.

Dr. **Goldstein**. OK, then I wouldn't. I think if we are all meeting in a spirit of true aspiration for the health of our society, that you guys have to trust us. What we are trying to do is do our best in medical research.

Although I think there are legitimate questions, truly legitimate questions as opposed by Mrs. Haire and other people in our society, the fact of the matter is that medical research conducted in appropriate environments is attempting, for all its worth, to find out the kind of answers you are approaching.

Mr. **Shamansky**. Are you satisfied overall with the progress?

Dr. **Goldstein**. I am somewhat satisfied. I think there are clear problems, many of which have been presented here today.

Mr. **Gore**. The questions concerning research are different from the questions involving use.

Dr. **Goldstein**. Not necessarily, Mr. Gore.

Mr. **Gore**. But we have the study by Dr. Brackbill and the experience of others. In her case, 70 percent of the ingredients consumed during pregnancy have no published reports on their safety or lack thereof. Yet, although most mothers knew they had taken a drug and why, some of them knew the name of it, none of them had any indication that there was a risk involved.

Now we are just not doing the job. Everything is not hunky-dory.

Dr. **Goldstein**. That is exactly the point I was making. We should conduct such research.

Mr. **Gore**. But at the same time they ought to be informed of what the risks are that they are facing and that the fetus they are carrying is facing.

Dr. **Goldstein**. That is true. I don't think any of us would disagree, to the extent possible. The question that was raised—and I think Mrs. Haire's statement, which she wishes to apply to the package—inserts that the risks of this drug are at present unknown is imminently useful.

Mr. **Shamansky**. Has the profession been pushing that insert?

Dr. **Goldstein**. I don't think so.

Mr. **Shamansky**. Why not?

Dr. **Goldstein**. Because there is an assumption made, and I am not casting aspersions, that the package insert has educational value.

Mr. **Shamansky**. What about the fact that the insert has no educational value? Is that sensible or not?

Dr. **Goldstein**. You two act like you are friends It is sensible, but I think if we just sit back and consider where education comes in and what the consumer does with small pieces of paper, that may or may not be included in the package. If you look at how people get their prescriptions, there is seldom a package insert. The package insert comes in a box to the pharmacist.

Mr. SHAMANSKY. Those are all mechanical details.

Mr. GORE. That is part of the problem.

Dr. GOLDSTEIN. I agree. There is no pharmacist here.

Mr. SHAMANSKY. If the medical and allied professions had a desire to get a message across, I cannot believe it is beyond the ingenuity of the manufacturers and the pharamacists and the profession to work out some code, color, whatever you want to do, to get a message across.

I am becoming amazed at the complacency of it all.

Dr. GOLDSTEIN. I have to argue with you, Mr. Shamansky. I think complacency is a very strong word. I think there is tremendous concern among our colleagues.

Mr. SHAMANSKY. How about effective action.

Dr. GOLDSTEIN. All us Brownian movement, just wiggling in place and not getting anything done, but we are trying to get something done and we don't have the tools.

Mr. GORE. I think what we are finding in this hearing is that although there is a debate over what Mrs. Haire charges, there really is no serious debate about the proposition that consumers for health reasons and for ethical reasons should be given much more information than they are now being given.

The only interest which stands in opposition to that to move is the financial interests of the pharmaceutical industry. That is all. There is no logical or ethical proposition which stands on the other side.

Dr. Cohen?

Dr. COHEN. Mr. Chairman, I just wanted to address one point and not have it lie there uncommented upon. That was the exchange that occurred a few minutes ago with Dr. Goldstein over the issue of the trial of a drug in a full-term pregnancy when the drug was going to be used in a premature pregnancy.

The response from the subcommittee was that it seems eminently sensible that that should be done. That response is a beautiful example of the head-on collision of both intellect and ethics coming from two separate directions.

It is unethical by our present standards, and to my knowledge, you attorneys had better correct it, by case law it is illegal.

Mr. SHAMANSKY. He is not a lawyer. I will clear that up right now.

Dr. COHEN. Unethical, and to my knowledge by case law it is illegal for an individual, a woman, to give consent for an experiment to be done on a minor under her guardianship when the procedure cannot have a possible benefit for that individual.

If the drug is designed to stop labor for a premature baby, the full-term baby cannot benefit from it. I am not telling you that is right or wrong, but I am telling you my understanding from the research I have done and the people I have discussed this with.

Mr. GORE. Are you talking about Ritodrine?

Dr. COHEN. That is right.

Mr. GORE. When it halts the onset of premature labor, are you saying the full-term infant cannot benefit?

Dr. **Cohen**. By definition, it is used to delay the delivery of the infant as long as possible to allow proper development to occur. If the infant is full-term, there is no benefit to that fetus to be in utero longer. I am assuming that that is what Dr. Goldstein was referring to.

Mr. **Shamansky**. I want to respond to that. That is one of those lovely dilemmas that I don't think is helpful to say because you reach a dilemma like that and it is an exquisite dilemma, therefore you don't do something.

Dr. **Cohen**. I am reflecting on the fact that his study was turned down by a committee operating under guidelines.

Mr. **Shamansky**. I am asking the profession to raise that question instead of passively accepting the fact that that is a dilemma. I admit there may be a legal barrier to that. Then raise the issue and say something about it.

Dr. **Cohen**. That was raised by the national commission several times.

Dr. **Yaffe**. I would like to move to this point of research, the question of all the drugs that have never been studied, the 70, 80, or 90 percent. The question of discussion I would like to raise is, who is going to pay for that? I would like to study them, but who is going to pay for that?

Under the system of drug development in this country, these drugs have been given approval for marketing, not in pregnancy.

Mr. **Gore**. We allow them to imply that it has been approved for use in pregnancy but we consciously mislead the American people into believing erroneously that it has been approved for use in pregnancy.

The medical profession ought to be as much upset about that as Mrs. Haire is, it seems to me.

Dr. **Yaffe**. Many of my colleagues are, and they do disclose. Mr. Shamansky, when I said sometimes disclosure is not complete, I never would fail to disclose that the drug has never been evaluated in pregnancy. That is an unknown risk I would also present to the patient.

I am talking about the rare side effects they think would be more upsetting to the patients. But the question arises about the 80 percent, 90 percent, it is actually higher, of marked drugs, that Dr. Brackbill surveyed in a study that are now being sold and obviously used during pregnancy. Who is going to pay for that kind of research?

Mr. **Shamansky**. Dr. Yaffe, I would like to respond in this fashion. Until the medical profession gets itself together to raise the question to the public and to the Government, I don't think you will ever get to that answer.

Mr. **Gore**. Well, we are raising the question now.

Dr. **Yaffe**. That has been raised. I have raised it many, many times, particularly as it also applies to children.

Mr. **Gore**. OK, I have a couple of other questions, but I will forgo them. I wanted to ask some questions about Ritodrine. Let me summarize what I understand to be the views of all three; that is, that there are serious questions raised by the use of Ritodrine that ought to be examined more carefully than they are being examined.

Can you address that real briefly?

Dr. GOLDSTEIN. You are right.

Dr. COHEN. I have no qualification to address it. I just don't know.

Dr. YAFFE. The effects, as I understand it, of Ritodrine upon the baby or the fetus have only been looked at in a short-term point of view. There is no question Ritodrine is efficacious so there is benefit in stopping labor, but no one has undertaken a long-term study of a cohort of infants exposed to Ritodrine for proper indication and seen what they are like 2 years later.

That is the kind of long-term study that we need.

Dr. GOLDSTEIN. Do you want more or are you satisfied?

Mr. GORE. If you could submit more for the record, we would be delighted to receive it.

Dr. GOLDSTEIN. The question again is one of controls, Mr. Gore, against whom will the outcome of babies who receive a drug given for premature delivery be matched. Will they be matched against other women with the same problem who don't receive the drug, and is that an ethically reasonable way to approach medical care.

Mr. GORE. The mothers who were given that drug now, are they given the information about the risks which may adhere to it?

Dr. GOLDSTEIN. A very large hospital with which I am intimately familiar uses another drug rather than Ritodrine for a variety of reasons, one of which was that three of the first five babies born under the influence of Ritodrine, after it failed, which all of the labor agents will, had blood sugars below ten milligrams per deciliter.

Mr. GORE. But now it is being used very commonly throughout the United States and mothers are not told that these risks exist.

Dr. GOLDSTEIN. I cannot answer for that. I just don't know.

Mr. GORE. OK. This is an awfully late lunch we are getting to, but we are going to break nonetheless. We will reconvene with our last two witnesses, Dr. Slone and the Honorable Arthur Hull Hayes, the Commissioner of the Food and Drug Administration.

We will reconvene at 2:45.

AFTERNOON SESSION

Mr. GORE. The subcommittee will come to order. Our next witness and next to last witness is Dr. Dennis Slone, codirector of drug epidemiology unit, School of Public Health, Boston University Medical Center.

Dr. Slone, we are delighted to have you today. Without objection the entire text of your prepared statement will be put into the record. If we had more resources at our disposal I would like to put the entire text of your book in the record but that would be an unreasonable request for the reporters and for the committee budget but we are going to try to get you to enlighten us based upon the voluminous work you have done in this area. We invite you to proceed at this time.

STATEMENT OF DENNIS SLONE, CODIRECTOR, DRUG EPIDEMIOLOGY UNIT, SCHOOL OF PUBLIC HEALTH, BOSTON UNIVERSITY SCHOOL OF MEDICINE

Dr. **Slone**. Congressman Gore and members of the subcommittee, first I would like to express my appreciation for having the opportunity to address you. Without further ado let me move directly to the purpose of my presentation today. It is to review the background factors related to chemical risks to the unborn child and recommend a strategy for the study of drugs to determine their safety, or lack of safety, in relation to the risk of birth defects. In view of the contents of the preceding testimony and in the interest of saving time I will omit the opening remarks contained in my written testimony and proceed straight to the heart of the matter.

What is known today is that certain drugs undoubtedly do harm the fetus. Thus while on theoretical grounds we should be concerned with the entire chemical environment, attention has been given primarily to drugs, particularly because of the dramatic and tragic disasters with Thalidomide and diethystilbestrol which have occurred in the past 20 years. In addition to these two agents, there are others which we know to be teratogens and they are listed in table 1.

I was taken aback by the testimony given by earlier witnesses as to some of the substances which are regarded as tetragens. I specifically refer to aspirin. In my view aspirin is one of the few drugs in which there is sufficient data available so that it is one of the very few substances about which you can make a definitive statement, that it is safe with respect to physical anomalies. You can virtually not make that statement with just about any other drug that you care to mention. However but with respect to aspirin I think that is a reasonably conservative thing to say. Now the list as shown on this chart starts with Thalidomide and goes on down the list with synthetic, progestogens, diethylstilbestrol, folic acid antagonists, and alkylating agents. The latter two are drugs used for treatment of cancer. Tetracycline is a widely used antibiotic. Warfarin is an anticoagulant and iodides are used frequently in the management of thyroid disorder. These eight or nine drugs are without question generally accepted across the board by all biologists as teratogens. I think it is safe to say that for the vast bulk of other drugs, there is no general agreement about the absence of effect.

Mr. **Gore**. This very short list is an exclusive list. Of those drugs not on the list, are drugs which can be described as known to cause birth defects?

Dr. **Slone**.This list enumerates those drugs for which you find general agreement across the board that they cause physical anomalies. For the rest of the drugs, our state of knowledge is that either there is controversy about the effect of a drug—a case in point for example is Dilantin or Phenytoin used in the treatment of epilepsy, or for the rest we simply do not have sufficient knowledge to make statements, clear cut statements about safety or adversity.

Mr. **Gore**. But this list does not address neurotoxics or behavioral effects.

Dr. **Slone**. My comments are addressed to defects you can see or that require surgical correction. I will make that clearer as my testimony evolves.

Against the background of repeated examples of drug induced catastrophe, we must attempt to provide systems dedicated to identifying drugs harmful to the fetus. The rest of this presentation will focus upon appropriate strategies to establish drug safety, or lack of safety.

Parenthetically it would be useful and simple if animal studies could unquestionably identify teratogens prior to their use in human populations. Unfortunately, such studies to date have proven unreliable in predicting the safety or risk of individual drugs. However, the obvious potential value of laboratory approaches, indicates a clear need to expand and continue experimental teratological research with a view to obtaining the earliest possible warning of potential trouble.

Given the present uncertainty of generalizing from animal experiments to the human fetus, it is my view that if we are to reduce the risk of human teratologic disasters such as we have already witnessed, there is a pressing requirement to develop and maintain a system of epidemiologic drug surveillance in human populations that should continue indefinitely. By epidemiologic surveillance, I mean the formal study of distributions and determinants of states of health—particularly birth defects—in human populations.

Before considering various epidemiologic strategies, I would like to review the stages of human embryonic development, since they influence the design of relevant studies. Figure 1 displays events over time from the period before conception, to birth. Before pregnancy, the genetic material contained respectively in the male sperm and female egg are susceptible to various influences. After conception, the most critical phase of development is when the organs are being formed. This phase of organogenesis is completed by the end of the third month of pregnancy. It is during this early phase that virtually all physical malformations occur. The latter two-thirds of pregnancy is the period during which the fetus grows and develops rapidly. In particular, the brain increases in size manyfold in only 6 months. Delivery, of course, is the final event.

Now with this diagram in mind it is possible to see that adverse influences can express themselves at each stage. I would like to digress for a moment and point out that witness after witness today has drawn attention to the fact that there are a wide range of abnormalities which can manifest themselves as a consequence of adverse influences during pregnancy. I think Mrs. Haire has emphasized and focused attention on the possible subtle but profound effects upon the functioning of a human being other than those related to physical malformations. I want to go on record as supporting her concern about those effects. I think she has done a service to contemporary society by highighting those possible adverse effects. I also wish to make the point, however, that all my comments and research has been devoted to one restricted period during pregnancy, namely, the period of organogenesis and I have no data on neurologic and behavioral effects.

The next poster is an overlay on the previous poster where it shows across the top, a series of environmental exposures with arrows indicating how different environmental factors influence various stages during gestation and how they might manifest. For example radiation can damage the genetic material before conception. If taken during the critical phase of early organ development, a drug—for example, Thalidomide—can produce physical malformations. This is demonstrated on the second vertical arrow in the chart showing how this can occur.

Viral infections—that is, herpes—during the second half of pregnancy can interfere with normal growth and development—particularly of the brain—and result in a large number of motor and mental disabilities. Finally, during delivery, there are the risks of obstetrical manipulations, as well as drugs, with damage ranging from mild intellectual impairment to more severe consequences such as mental deficiency, cerebral palsy, or even stillbirth or perinatal death.

In order not to confuse an area which is complex to begin with we should try to determine what effects we are talking about. Furthermore, what period of pregnancy we are addressing. We should separate the period prior to conception, where you express an effect via the gametes, from active organ development, and growth, particularly of the brain, in the latter half of pregnancy. I think if we keep these issues separate, it makes it easier to understand what strategies are called for and where the major problems really lie.

Thus our concern about potential adverse effects of environmental factors cannot be limited to the embryo alone; rather it must extend from the period prior to conception, through gestation to delivery of the newborn infant.

Obviously, the range of disabilities which might occur as a result of injury in each of these discrete periods is wide. Indeed, in the area of birth defects we are not dealing with a homogeneous and uniform disease entity, but a spectrum of conditions not unlike the various diseases seen in adult populations. Consequently, each specific malformation must be studied as a discrete outcome. These considerations influence the design features of any study proposed to identify teratogens or to demonstrate safety. As an aside I think there is a tendency among us working in the field to consider birth defects or malformations as one particular disease. Nothing could be further from the truth. You cannot regard malformations as a singular outcome but rather a wide spectrum of different diseases, and it adds to the complexity of what we are trying to do. My concern today is with the period of early embryonic development, and the design and deployment of an appropriate surveillance program to evaluate the safety or adversity of drugs used during pregnancy, and I will confine my attention mainly to physical malformations arising during this period. This objective of surveillance is briefly restated in figure 3.

To consider further how to plan such surveillance, we need some insight into the dimensions of the problem of birth defects and drug usage in pregnancy. Based upon the data collected during the collaborative perinatal project, a large followup study conducted in the United States between 1958-65, we estimated that the rate of major malformations among 50,282 children was approximately 3 percent. Major malformations were those that were life-threatening, that required surgery, or that constituted serious cosmetic defects. Extrapolated to present day conditions, among approximately 3,350,000 infants born each year in the United States there are some 100,000 with major malformations. The overall figure of 3 percent encompassed a very wide range of specific malformations. Of course, each individual malformation occurs much more rarely than 3 percent, and five examples are given in table 2. Clubfoot is among the more common birth defects—2.4 per 1000 births—so that there would be about 8000 cases born each year in the United States.

Other important birth defects are even more rare. Cleft lip, for example—about 1 per 1,000 births—occurs in about 1,500 children each year, and tracheoesophageal fistula—an abnormal opening between the trachea and esophagus—occurs in one in 10,000 births, leading to slightly over 300 cases per year. Thus, although major malformations, overall, are a serious public health problem, affecting about 100,000 infants each year, each individual deformity is rare or exceedingly rare. These facts are particularly relevant to the issue of appropriate design of drug surveillance for teratogens.

The other relevant point is the prevalence of drug use in early pregnancy. According to our own data the average pregnant woman uses between two and four different drugs during early pregnancy, frequently before she knows that she is pregnant. Table 3 gives, for nine drugs, the percentage of use as derived from our current "Birth Defects Interview Study" (BDIS). Tylenol—acetaminophen—is by far the most commonly used drug, taken by 37 percent of pregnant women during the first trimester of pregnancy. Generalized to all pregnant women, this means that about 1,400,000 use the drug each year.

Tylenol represents one extreme. At the other and more typical extreme, most drugs are used by considerably less than 1 percent of pregnant women. A typical example is Hydrodiuril—a diuretic—at 0.6 percent it would account for about 20,000 exposures annually. In between that I will go down the list to highlight them. You have Bendectin used by some 25 percent of women. Aspirin, Diazepam, Propoxyphene, Fiorinal, Compazine, Hydrodiuril, and Seconal.

Mr. GORE. Bendectin is second only to Tylenol?

Dr. SLONE. Yes. It is used by 25 percent of all women.

Mr. GORE. Twenty-five percent of all pregnant women in the United States.

Dr. SLONE. Yes, sir; that is our most recent figure from information derived in the past year.

Having briefly considered the dimensions of the problems in terms of the rarity of malformations on the one hand, and the frequency of drug use in pregnancy on the other, one can consider the research options. To do so it is helpful to begin by considering in general terms, existing or potential sources of information. As shown in the next poster, information concerning drug effects is derived from animal experiments, human case reports or so-called spontaneous reports which are sent to FDA by the drug companies or published as letters in medical journals, clinical trials—experiments involving random allocation of patients to treatment groups—and observational—non-experimental—epidemiological studies.

Experimental research strategies have serious limitations. As already mentioned, findings in animals at present cannot readily be generalized to human beings, and clinical trials designed to determine malformation rates in humans are out of the question on ethical grounds. Therefore, the only realistic options are case reports and epidemiological studies.

Case reports can be useful, but they can also be misleading. As indicated in the first line of table 4, there are approximately 3,350,000 births occurring each year in the United States, of which approximately 3 percent, or just over 100,000 infants, are born with major malformations. If we assume that 5 percent of pregnant women—one in 20—use a particular drug, 167,500 women would be exposed. If that drug had no harmful effect whatever on the fetus, one would still expect a baseline malformation rate of 3 percent, resulting in 5,000 malformed infants being born to those women. Is that clear?

Mr. GORE. Yes. In other words a lot of women who use a particular drug are going to give birth to a malformed child even if the drug does not cause it at all.

Dr. SLONE. What I am trying to show on the slide is the order of magnitude of how many such women it will occur in any 1 year. With the relatively modestly used drug, 5 percent use you have 5,000 opportunities there for that drug to be implicated. Now more emphatically as shown on the last line if a drug is used by 25 percent of pregnant women, 837,500 women would be exposed; we would expect that they, too, would have a 3-percent malformation rate and that they would give birth to 25,000 malformed infants, even through the drug did not cause the defect. Since 25,000 malformed children are born to mothers exposed to this drug, the likelihood of someone observing the connection and reporting it is high, despite the fact that the drug is not teratogenic. I want to emphasize I am not apologizing for the use of drugs during pregnancy. I just want to highlight the intrinsic difficulties of making inferences of causality in the face of the methodologic problems we are confronted with. The 3-percent figure is the basic malformation rate.

Mr. GORE. You said earlier in your statement that the cause of 65 percent of all malformations is unknown.

Dr. SLONE. Yes.

Mr. GORE. And a good portion of that 65 percent could be associated with drug use?

Dr. SLONE. Yes.

Mr. GORE. So it would be inaccurate to conclude from this methodology that the 25,000 opportunities to implicate a drug that is used by 25 percent of pregnant women are all background. Some of that background may in fact be related to the use of the particular drug.

Dr. SLONE. It might well indeed. I am not drawing any conclusions I am merely outlining some of the basic difficulties.

Mr. WALGREN. When you pick up 3 percent rate among a population using Bendectin or Tylenol and you say that that does not allow you to infer causation because of the overall rate of birth defects in a general population, because of the point Mr. Gore makes it also does not allow you to infer noncausation.

Dr. **Slone**. I have not reached the point of making any inferences yet. I am still outlining basic things we have to worry about. What you can do is you can compare the amount of drug use for example in a particular malformation with the amount of Bendectin used in another group of infants. If you came out with 50 percent use in the one malformed and 25 percent in the other you could in fact make the inference Bendectin was responsible. We are not at the point of making inferences. I am merely alluding to the fact that if we rely on spontaneous reports to tell us about whether a drug is safe or not I would like everybody to appreciate the fact that there is ample opportunity just on the basis of these figures and understanding that 1 out of every 4 malformed children will have a mother who used Bendectin, or 1 out of every 3 children that is born malformed will have a mother that used Tylenol. I am saying that sets the stage on which we have to develop more sophisticated approaches. If I can proceed I think that will emerge.

It follows that in situations where drugs are used commonly in early pregnancy there is an extensive opportunity for the inappropriate implication of drugs as teratogens, and therefore case reports have relatively little utility. Conversely, when both the drug and the malformation are extremely rare, case reports have their greatest usefulness. Turning to epidemiological studies, there are two basic research options, called respectively the cohort and case-control approaches. In a cohort study pregnant women are enrolled, their drug exposures—use of a drug—are recorded, and they are followed. You will note that the malformation rates in exposed and unexposed infants can then be compared after the mothers have given birth. In the example shown the 100 women enrolled give birth to three different malformed children. Each dot is colorerd differently. You will notice in following 100 women at great expense and trouble we end up with 97 normal children. That does not provide us with any information with respect to malformation and the yield—to use a crude term—is only three malformed children we can study with respect to knowing whether drugs were in any way related. It is important to note that even large cohorts yield a very small amount of relevant information. To illustrate a cohort of 100,000 women would yield 97,000 normal infants, providing little useful information on malformations. The purpose of showing this illustration is to emphasize once again that the setting up of a multimillion dollar program of following up hundreds of thousands of pregnant women with respect to malformations and drugs would be a very poor cost-effective way of doing things. The collaborative perinatal project was the largest cohort—50,282 mother/child pairs—ever studied. Our group analyzed the data on drug use and malformations, and the results have been published. Our extensive experience with this analysis convinced us that while the cohort approach has some limited usefulness for assessing major malformations overall, it is insufficient for surveillance of drug effects in pregnancy in relation to specific—and usually rare—malformations.

This brings us to the second research strategy, the case-control approach. The next diagram tries to represent this. It traces its principle features. It is characterized by first identifying children with specific malformations for example such as cleft palate. What we do here is we start with the disease under study. We do not enroll a group of people and watch to see what happens. We start with a disease under study. In this instance there are four examples. We observe children with cleft palate, with absent limbs, with heart defects and children with spinabifida or failure of the spinal column to fuse. Then we go back and interview the mother and obtain detailed information on what drugs these mothers used within a few weeks of having given birth to these children. As the arrow indicates we go back to interview the mother of these children. Rates of maternal drug use among infants with certain defects are then compared with drug us of mothers of other infants. In answer to two earlier questions, let us assume we looked at cleft palate. We would know then that if we interviewed the mothers of 500 children with cleft palate we would expect 25 percent of those mothers to give us a history of having used Bendectin. We would compare that to the mothers perhaps of children with spinabifida or any other group of other malformations. If we found the rate of use was 25 percent in all of these mothers it would not be unreasonable to make the inference after proper and careful analysis that there was the same rate of Bendectin use in the malformation under study as there was in control or comparative subjects. Under those circumstances you could make the inference that Bendectin was not related causally to the malformation under question.

If on the other hand there would have been a big difference in the rate of Bendectin used among these groups you would make the inference that this drug may be related to the defect under study.

Two continuing studies, using this approach, are being conducted at present in the United States, one by the Center for Disease Control in Atlanta and the other by our group in Boston. Details of the latter study are described in an accompanying paper titled "Birth Defects Related to Bendectin Use in Pregnancy," which I did distribute with my testimony. If it is all right with the subcommittee I would prefer not to describe that again.

I would like to digress for a moment. If you accept my figure of 3 percent serious malformations at the moment this country sees about 100,000 to 150,000 children born each year with malformations. We have a study operating in three centers in the United States and Canada. It is expensive and it is difficult, and yet with all this effort we are barely managing now to study less than half of 1 percent of all the malformed children born annually. In other words we are studying something like 750 malformed children per annum which is a tiny and in my view pitiful fraction of the total burden of malformed children in this country, particularly when you consider there are over 200 discrete malformations in the general rubic of major malformations. Now the relative efficiency of the cohort and case-control designs is illustrated in the next slide. It demonstrates that with much smaller numbers, and at much less expense, the case-control design affords greater power. Larger numbers of cases of individual malformations can be more rapidly obtained than is realistically feasible using the cohort approach. Furthermore, whereas in a cohort study the malformation rate is predetermined by the size of the cohort—and it is expensive to enlarge a cohort study—the acquisition of cases of interest in a case-control study can be specified, and if desired, speeded up depending upon what you are worried about. You have no such flexibility present under a cohort study.

Based on our experience thus far with both approaches, our clear preference is for the case-control design. We hold this preference despite some potential drawbacks to the method, the most important of which is whether a mother's memory of drug use in early pregnancy is reliable. The problem, briefly, is that the mother of a severely malformed child may remember her drug use differently as compared with the mother of a normal child. We believe this problem can be largely avoided by comparing children with a specific deformity (cases) with children with other, very different, deformities (controls). For example, cases with cleft palate can be compared with controls with other malformations. The similar emotional impact on the mothers of the various deformities reduces the likelihood of recall bias. Such bias can be further reduced by the use of highly structured and detailed questionnaires. We have data that show how this potential bias can be reduced, and we believe that the concern with memory bias can be largely overcome by careful attention to study design.

With the case-control approach just described, it is possible to monitor a wide range of specific malformations, together with a wide range of drugs taken in early pregnancy. Such a system makes it possible to identify previously unsuspected associations between drugs and deformities.

It is worth stressing the limits to the interpretability of epidemiological data. Of course, the desire for clear and absolute answers on matters concerning birth defects is easily understandable. Unfortunately, however, absolute measures of risk, or of safety, simply do not exist in biological systems.

Estimates of human safety or risk can only be expressed as a range. For example, we might identify a given drug as increasing the risk of a malformation by fourfold, but we know that this estimate of fourfold may in fact range, for example, from as little as twofold to as much as sevenfold. As we collect more data, our estimates become more stable and we become more confident in them, so the range becomes narrower.

Just as estimates of risk are expressed as a range, so are estimates of safety. Thus, while a given study may show no apparent effect of a drug, we know that such an estimate is imprecise, and as scientists we acknowledge that we might have missed, in any one study, protective effects of the drug on the one hand, or teratogenic effects on the other.

By and large, the best attainable estimates of safety include increases in risk of as high as 50 percent. Thus, while we can rule out large increases in the risk, such as a doubling (100 percent) or more, we cannot confidently rule out much smaller increases.

With these limitations in mind, however, we believe that studies of human populations, based on epidemiologic approaches, can offer considerable information regarding the risks of malformation due to drugs taken by pregnant women.

I would like to add one or two comments if I might concerning some of the comments that I have heard earlier today by other scientists offering testimony. It has been repeatedly stated that the Food and Drug Administration should disclose information, should provide additional statements regarding safety or danger and FDA is somehow delinquent in not providing this information. I believe FDA has been given an impossible task. FDA is expected to regulate drugs, it is expected to provide information, but at the same time in my view—and this is based upon over 15 years of working with the FDA in this area and receiving funding from them in part—whereas they have tremendous demand placed upon them, they do not have adequate resources provided to pay for the kind of research that is necessary. Thank you very much.

Mr. GORE. Thank you.

Mr. Shamansky?

Mr. SHAMANSKY. Thank you, Mr. Chairman.

Dr. Slone, I think the Government is currently spending less than $1.5 million on epidemiology.

Dr. SLONE. I am very much aware of that.

Mr. SHAMANSKY. As a student of public health, what is a realistic funding level required to execute the needed epidemiological studies in this field?

Dr. SLONE. It is hard for me to answer that because anything I say might be seen as being self-serving. All I can tell you is that the Bureau of Drugs, as far as I know, in the past 5 years its total budget, much of which went for epidemiological research, was no more than $2.5 million.

My informant tells me, subject to correction, that over the past 5 years this amount has not been increased or adjusted for inflation and they have the same amount available this year as they had 5 or 6 years ago.

Mr. SHAMANSKY. Would you have any reason for that situation? Is it just a stepchild or is there pressure not to have it do something?

Dr. SLONE. I have no idea why funding has not been provided. FDA, when confronted by this, would generally say our general national budget is not ample to provide more.

Mr. SHAMANSKY. Somebody sets the order of priorities in any budget at FDA?

Dr. SLONE. Yes. I cannot speak to that. I have no idea.

Mr. SHAMANSKY. Is there any pressure from your colleagues in the medical profession to have that budget increased?

Dr. SLONE. I think the average person in the medical profession is so preoccupied with practicing medicine that they don't have any insights into what has to be done or what priorities are necessary in the area of setting public policy.

Mr. SHAMANSKY. How about academic medicine?

Dr. SLONE. Even the academic folks spend a great deal of time practicing though, as you saw this morning, they are generally aware of the problems. I don't think there is an effective lobby. I am always astounded at how the medical profession does not represent public health issues effectively. I don't understand it. I share your chagrin at why it is not effectively enunciated.

I don't know what the appropriate sum of money is. I cannot help but be aware of the current climate of reduced spending that seems to be fashionable. I would like to echo what Dr. Ryan said and that is that the most expensive disease that you can have in society is one that begins at the moment of birth and has to be carried through an entire lifetime.

I don't know what the cost to the United States and society is of some 120,000 malformed children each year in terms of economics. In terms of human misery it is incalculable.

All I can tell you is that the malformation part of our studies costs approximately $1 million a year. The bulk of that comes from private industry. I think it should be part of the record that the malformation study that I described today and the data I have shown you comes from a study that is in the main funded by Hoffman LaRoche. This was funded initially in 1976 when they were concerned about the allegation that the drug diazepam—valium—might be the cause of malformations and they requested a study to be done in order to clarify that issue.

That study is still under way and no definitive results have emerged. It was designed in such a way so we did not exclusively look at diazepam, but looked at the entire spectrum of drugs. That has cost a great deal of money.

The Food and Drug Administration does provide core funding for our general study which encompasses many various aspects of drug induced diseases.

Malformations are just one part of what we do. Insofar as the Food and Drug Administration has, over the past 5 years, provided 50 percent of our core costs, it is fair to say that the Food and Drug Administration must share the responsibility for funding this malformation study.

The direct costs for that malformation study have come from industry.

Mr. GORE. I might note that the relevant budget in question is being cut from $1.5 million to $1.1 million.

Dr. SLONE. Yes.

Mr. GORE. Mr. Walgren?

Mr. WALGREN. I wanted to ask when you move from the cohort study to the case control study, you really get very specific as to the defect and one of the statements that struck me is that perhaps drugs can cause a range of defects, particularly——

Dr. SLONE. That is a miscomprehension. We do not become specific. We steer the system but we interview every single different malformation we can get in an area.

We blanket an area and we try to identify every malformed child and we try to cover the widest possible range of malformations.

Mr. WALGREN. Solely on malformations. You are excluding anything like spontaneous abortions?

Dr. SLONE. Yes.

Mr. WALGREN. You are excluding, I am sure, on the kinds—perhaps things that are not considered as severe.

Dr. SLONE. Mental derangements in functioning or motor. We have not studied that. That is a totally different thing. It is a legitimate and important area, but we cannot study everything.

We have retricted ourselves to what we think is the most important area initially. That is phyical malformations, but correlated to what you have said is that one of the limitations we see to our study is the fact because we are only studying 700 or 800 malformed children per year the range of malformations that we can trap in our system and evaluate is limited by small numbers.

If you asked me to do what I thought was the best job for the United States, I would say we should be studying between 3,000 and 5,000 malformed children each year but I cannot foresee in the near future having the funds to do that.

One nurse interviewer deployed in the field can conduct between 200 and 300 interviews per year maximum. That means finding them, chasing them down, getting permission from the doctors, permission from parents, setting up interviews, traveling to people's homes, doing the interview, and so forth.

So it means that for every 1,000 malformed infants that need study, you need three full-time nurse interviewers in the field, so you can see what kinds of costs we are dealing with.

For every three interviewers you have in the field, you need a group of people at the central facility in order to process the data and administer the study.

Mr. WALGREN. That is on case control?

Dr. SLONE. On case control.

When you talk about cohort study, the order of magnitude of expense goes up by a hundredfold.

Mr. WALGREN. What is so expensive about the kinds of broad informational gathering of data that would go up a hundredfold on an individual case?

Dr. SLONE. The cohort study is very inefficient. For every 100 women you would enroll in a cohort study, only three would be malformed. You have 3 percent yield.

We have already spent 200 million dollars conducting a cohort study. You have on file a book that was published as a consequence of that analysis. That analysis was frustrating because we ended up with essentially fewer malformed children from 55,000 pregnant women than we currently have after a couple of years of modest effort applied to starting with malformed children rather than following the pregnant mother.

Mr. GORE. The cost associated with such a cohort study might be reduced significantly by piggybacking data from HMOs and Medicaid, is that not correct?

Dr. SLONE. Yes, you could do that. I am not adverse to using other resources.

For example, Keiser Permanente in Los Angeles has a very large group of people they provide medical care to. Perhaps one day in the future that resource could be utilized, but once again, HMOs can provide basically the same two kinds of data.

You can take HMO information and use it in a case control mode. You can say we will look at all malformed children that this HMO identifies or you can look at it from the point of view of following the mothers themselves. The inherent limitations I described of these two approaches are still present. The source of the data makes no difference.

If you have 10,000 pregnant mothers, you are going to end up with 500 malformed children no matter how you slice it.

You have small numbers problems. Once again I know you are interested—for example, you indicated in your letter you were curious about the kind of risk estimates you can place around a particular drug. Let me emphasize where you have tiny numbers, statements you make about safety or nonsafety then have such enormous ranges around them they are not terribly useful.

That is a function simply of numbers. One cannot overemphasize that in this particular circumstance what we really need is a study which will have sufficient material so we can make estimates that are fairly tight and that can be used properly by public health authorities, by the Food and Drug Administration.

Mr. WALGREN. The difficulty I have is that if you were to assume that a drug could cause different kinds of birth defects, and then you rule out some of those birth defects such as whatever might trigger a miscarriage, that you then would reduce the incidence in the ones you actually looked at down to such a degree that they would get lost in the normal expected frequency of birth defects. We would have missed putting our finger on causation. Does that trouble you?

Dr. SLONE. It doesn't trouble me, because all we know concerning animal effects, a proven experience in the human population, is drugs virtually never cause malformations across the board. They are always of one sort and perhaps with overflow to one or two other systems. We use such a wide range of malformations ranging from serious to trivial, such as inguinal hernia, that we are reasonably confident we are not missing low level teratogens in this approach. We are reasonably confident we are not missing something that is causing every single conceivable malformation. You have to postulate the drug was causing virtually over 50 or 100 malformations with equal frequency in order for us to lose sight of a teratogen under those circumstances.

Mr. WALGREN. So you are saying the studies you are involved in are so inclusive in their definition of birth defect they are going to pick up what you would expect?

Dr. SLONE. I think initially they are going to pick up birth defects that are reasonably common, that we have sufficient information on, as the study expands and becomes institutionalized and as we are able to study greater malformations.

Mr. WALGREN. Let me ask you this. Was closed bladder—were they included in your Bendectin malformation study?

Dr. SLONE. We only addressed in that study two malformations. We looked at a spectrum of cardiac malformations, and we looked at cleft anomalies. There are any number of other anomalies we do not have enough information on to make a statement about. We hope, over time, as we continue to collect malformations we will continue to publish papers on Bendectin and other malformations and show there is an association or there may be an association. But at the moment the data is not available to address that issue.

One of the reasons why I think it is urgent for this study to be expanded to an order of magnitude commensurate with the needs is because we need to be able to look at some of the rarer malformations that we can't address at the present moment.

Mr. GORE. Thank you. I have a couple of brief questions, and then we will move on. What about a study to establish a base rate among women who use no drugs during pregnancy? Has that been attempted?

Dr. SLONE. You are talking about the cohort. If one were to go the cohort way, you would want to include the group of women.

Mr. GORE. But it has not been done.

Dr. SLONE. In the book we have there were a small number of women who had not used any medication, but it is tiny. I think in the case-control study we do find women who have used no drugs whatsoever.

Mr. GORE. Now isn't it true that both the case-control approach and the cohort method make it difficult, if not impossible, to pick up problems associated with new drugs in a reasonable period of time?

Dr. SLONE. I think that is very difficult. As a new drug comes on the market, it has to penetrate the market sufficiently in order to express its effect before we can pick it up.

Mr. GORE. The deficiencies of the only available epidemiological approaches enhance the importance of drug experience reports provided by the pharmaceutical companies, don't they?

Dr. SLONE. But the nature of drug experience reports, however, in pregnant women, once again, are saddled by the slides I showed earlier where, for example, there is a certain baseline expected, malformation rate you would observe. The only situation where case reports are useful is where you have a rare malformation, a strange malformation and rarely used drugs. The coexistence of reports of rare malformations in association with rarely used drugs has a lot more importance because as you can see from the illustration where a drug is only used by one-tenth of 1 percent and the malformation is extraordinarily rare, the probabilities of those reports coming in due to some totally chance association are obviously much less than in the drug which is used commonly and in a malformation which occurs commonly, so spontaneous reports have a role to play.

If you wanted to certify a drug for specific use in pregnancy, you could require all women who used that particular drug to be followed so what we call the restricted focused cohort for only those women who only use that drug makes some sense.

Mr. GORE. As far as you know, has FDA ever required such a study?

Dr. SLONE. As far as I know, no. But my knowledge in this area is incomplete.

Mr. GORE. The statistics and the numbers can have a numbing effect but different sorts of lessons can be derived from studies such as yours by circumscribing the areas of uncertainty and the areas within which debates are raging. You can also highlight the importance of information upon which we can rely and the vast amount of uncertainty enhances the importance of information such as that derived from timely drug experience reports and makes it all the more important that companies provide them and not sit on them or in any other way screen them because each one of them has the importance magnified many times over by the very uncertainty that is associated with the other epidemiological evidence that we have available.

So although we can be numbed by the statistics, we can also learn from them. I have some other questions but I think I will forgo them. We appreciate the excellent testimony you have provided and the work you have done really remains the most definitive in this field, and we appreciate your contribution today.

Mr. **Gore**. Next we have Hon. Arthur Hull Hayes, Jr., M.D., Commissioner, Food and Drug Administration; accompanied by Marion J. Finkel, M.D., Associate Director for New Drug Evaluation; and Judith K. Jones, M.D., Ph. D., Director for Division of Drug Experience.

Dr. Hayes, it is always a pleasure to have you appear before the subcommittee. I had some kind words for you earlier in the proceeding which I shan't repeat on this occasion, but I have been most pleased with our working relationship and I am delighted to have your testimony on this matter.

Without objection the entire text of your prepared statement will be put into the record. Do the other participants have statements also?

STATEMENT OF HON. ARTHUR HULL HAYES, JR., M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY MARION J. FINKEL, M.D., ASSOCIATE DIRECTOR FOR NEW DRUG EVALUATION, BUREAU OF DRUGS, FDA; JUDITH K. JONES M.D., PH. D., DIRECTOR, DIVISION OF DRUG EXPERIENCE, BUREAU OF DRUGS, FDA; AND TOM SCARLETT, CHIEF COUNSEL

Dr. **Hayes**. They do not, Mr. Chairman.

Mr. **Gore**. Please proceed with your presentation.

Dr. **Hayes**. Thank you, Mr. Chairman, and thank you for your previous remarks. I will look forward to reading them in the transcript.

May I at this time, in addition to my colleagues who accompany me, introduce Mr. Tom Scarlett, Chief Counsel for the Food and Drug Administration, who is with us here today.

Mr. Chairman, I am pleased to accept your invitation to appear at this important hearing. In the past several years, we have witnessed an increased awareness by physicians and other health professionals and by prospective parents in the safety and effectiveness of drugs used in obstetrical practice, particularly those used in women during labor and delivery. The primary focus of this awareness is on the potential risks these drugs may pose to the health and well-being of unborn and newborn infants. We at the Food and Drug Administration (FDA) share this concern, and I am pleased to have this opportunity to describe our policies on drugs which may be used in pregnant women and during labor and delivery.

I should start by expressing a well-known axiom that no pharmacologically active substance is completely free of risk. Thus, any active drug which is capable of exerting a pharmacological effect carries with it some potential to produce untoward effects. In most instances, the untoward or unwanted effects occur in the same person who takes or receives the drug and in whom the intended effect is directed. In such cases the benefit/risk determination is relatively straightforward. The question is, do the potential benefits from the drug to help in diagnosing or treating a particular disease or condition outweigh its potential to produce harm or undesirable effects. In drugs used in pregnancy and during obstetrical practice, the benefit/risk considerations must take into account the potential of a drug, intended to help the mother, to cause an unwanted or undesirable reaction in her child. In evaluating a new drug for marketing, the agency attempts, within scientific limits, to assess the risks and benefits. The results of the assessment are communicated to physicians in the official labeling of the drug. This labeling is carefully reviewed with the drug's sponsor prior to approval so that each product can be used in a way to maximize its therapeutic potential while minimizing its risk.

Since the early 1930's, FDA has been aware of fetal damage resulting from various environmental agents to which the mother was exposed such as X-radiation and rubella virus infections. Aminopterin, a drug marketed in 1951 for treatment of acute leukemia, bore a strong label warning against use in pregnant women. The warning was based on adverse effects in animal reproduction studies which included abortifacient effects and abnormalities in the embryo.

Teratogenic effects in the human infant were subsequently demonstrated by the birth of severely malformed infants as a result of unsuccessful use of the drug to induce abortion. This was one of the first drugs demonstrated to have teratogenic effects in humans and the effect had been predicted from animal reproduction studies.

Adverse effects on the offspring may include teratogenic effects during critical early periods of organ development in the fetus; pharmacologic or toxicologic effects of the drug during or immediately following exposure; or delayed effects which may become apparent months or years after exposure. An example of delayed effects is the development of adenocarcinoma of the vagina in teenage girls and young women as the result of their mothers' exposure to diethylstilbestrol, DES, during pregnancy.

We believe that increasing public and professional awareness of these potential effects has been a contributing factor in the decreasing use of drugs both in number and dosage during labor and delivery in recent years. I am equally convinced, Mr. Chairman, that the judicious use of effective drugs in association with improved obstetrical care, advances in monitoring techniques, and in care of preterm and newborn infants, has contributed to the decline in maternal and neonatal mortality over the past two decades. Approximately 20 years ago, the maternal mortality rate was 37 per 100,000 live births; today it is less than 8 per 100,000. Neonatal mortality during the same period has declined by nearly half. The paradox is that technological advances in products and procedures for obstetrical care have themselves raised new questions concerning their safety and effectiveness. It is appropriate that the public be informed of these issues, since the level of risk which is acceptable to society as a price for the benefits derived from these scientific advances is indeed a public policy issue.

FDA policies and programs relative to fetal protection have developed along several lines: animal and human testing requirements to establish safety and effectiveness of new products for marketing; benefit/risk decisions on approvability of drugs for marketing; preparation and dissemination of labeling and other information on these products; conduct of postmarketing surveillance to determine the incidence of known adverse effects, and to detect previously unsuspected adverse effects; and review of new information on potential fetal risks derived from various sources, followed by actions appropriate to the findings. In describing these programs I will also outline the limits which confront us in certain areas.

FDA's investigational new drug regulations and clinical guidelines require that before a new drug can be studied in humans, the manufacturer must submit evidence of the drug's identity and purity; the results of pharmacological and toxicological studies conducted in animals; the results, if any, of human experience from clinical trials conducted outside the United States; and a reasonable plan for studying the drug in humans. With few exceptions, women of childbearing potential may not participate as subjects until reproduction studies have been completed in at least two animal species.

FDA guidelines for reproduction studies in animals are designed to determine effects of drugs on the entire reproductive process, including the effects on fertility in the male and female, conception and implantation of the embryo in the uterus, development and survival of the fetus, the birth process, and the survival and well-being of the offspring.

Women of childbearing potential who are not pregnant may participate as subjects in the clinical trials if the reproduction studies in animals do not reveal any potential for adverse effects on the reproductive process and if reasonable safety and evidence of effectiveness were demonstrated in early studies in men and postmenopausal women.

To participate in such clinical trials patients must give their informed consent, which includes their understanding of the nature of the investigation and the potential risks they may incur. Animal reproduction studies do not always predict potential human teratogenicity, therefore, a woman's informed consent to participate should be based on a clear understanding that a lack of teratogenic effects in the routine animal tests by no means guarantees safety for the human fetus. For drugs other than those used for a condition related to pregnancy, FDA's clinical guidelines advise that pregnancy tests be performed prior to introduction of an investigational drug in women of childbearing potential, and that the patient be informed of suitable contraceptive measures. The guidelines also recommend that, when women become pregnant during a study, fetal and perinatal followup should be conducted.

With the exception of drugs specifically indicated to treat a condition resulting from pregnancy, such as eclampsia or premature labor, or drugs used during labor and delivery, pregnant women are usually excluded as research subjects in studies of investigational drugs. The involvement of pregnant women in research raises the still unresolved issue of legally valid informed consent for the unborn child to be itself involved in research not intended for its benefit. The result is that controlled clinical trials in pregnant women are ethically justified only for drugs intended for treating conditions specifically related to pregnancy, since only in that population can effectiveness of the drugs be established and the risks for both the woman and fetus be defined. Such treatment, when successful, can be considered of benefit to both the woman and the child. These drugs are few in number, however, and the majority of drugs cannot be assessed for fetal safety in clinical trials prior to marketing. This is true even though once on the market the drug may be prescribed for use in pregnant or potentially pregnant women in need of treatment for the condition for which the drug is indicated.

This policy reflects departmental regulations regarding the protection of pregnant women and the fetus as research subjects. The regulations are based on the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The regulations specify that, if the general requirements are met, including informed consent, a pregnant woman may participate in research if its purpose is to meet the health needs of the mother and the risk to the fetus is either minimal or is limited to that which is necessary to meet the mother's health needs. We have interpreted this to include research only on investigational drugs or devices employed to diagnose or treat a condition related to pregnancy, labor, or delivery.

Drug research in general does not meet the requirements of minimal risk to the fetus since animal studies are not totally predictive of potential risk. As one means of addressing this dilemma, the FDA has recently taken several important steps designed to improve the reliability of animal tests as predictors of reproductive and teratogenic effects in humans. A reproductive toxicity risk assessment group has been established under the auspices of the interagency regulatory liaison group, IRLG, to develop criteria to support consistent interpretation and utilization of teratologic data from animals and humans. The group will arrive at a consensus of such questions as: what data are required to determine that a substance poses a teratogenic or reproductive hazard to humans; what are the criteria for evaluating data; what is the best design for the conduct of animal experiments; and how accurately do animal tests predict human hazard? To assist in this endeavor the IRLG will hold a workshop on reproductive toxicity risk assessment at FDA on September 21-23, 1981.

FDA's National Center for Toxicological Research (NCTR) is conducting an interlaboratory study to evaluate the reliability and sensitivity of a group of animal tests that detect postnatal behavioral effects induced by prenatal exposure to chemicals. These behavioral tests may provide evidence for teratogenic effects more subtle than the anatomical changes which are the endpoint of conventional animal teratology testing. When reliable methods are developed which will yield valid data relating to human infants, they will be incorporated in FDA's guidelines for animal reproduction studies. Furthermore, as new preclinical technology improves risk detection it may be possible to expand the kinds of clinical trials in which pregnant women can participate.

In cooperation with the IRLG, NCTR is also evaluating the usefulness of short-term teratological prescreening tests to establish priorities for further testing of chemicals.

In addition, FDA scientists participate in some of the working groups of the IRLG in the United States and the multinational Organization for Economic Cooperation and Development, OECD, that are involved in the preparation of toxicity testing guidelines, including those for reproduction and teratology. These guidelines, when adopted, will result in use of uniform-testing criteria for chemicals by a large portion of the developed world. Presently, the IRLG has guidelines published for teratology studies and has published for comment guidelines for reproduction studies.

To optimize the design and conduct of clinical trials of investigational drugs, FDA concluded that written guidelines which provide the current testing approaches that experts consider desirable should be developed for drug companies and investigators. To this end, FDA and its scientific advisory committees have developed over 25 clinical guidelines for the study of various drug classes in humans. Where appropriate, specific advice is given on tests to be conducted in pregnant women and their offspring exposed to an investigational drug, as, for example, in the Local and General Anesthetic Drug Guidelines.

As you are aware, Mr. Chairman, anesthetics, particularly local anesthetics, are widely used in delivery. The Anesthetic Guidelines, recently updated by our Anesthetic and Life Support Drugs Advisory Committee, provide that, in obstetrical patients, studies should be directed to determine effects on the fetus, such as placental transfer of drugs, respiration and short-term neonatal neurobehavioral effects.

The question has been raised by some whether long-term neurobehavioral tests involving up to 7 to 10 years of followup of the offspring should be conducted.

These tests would be used to detect possible delayed effects of the drugs on mental activity and behavior. Our Anesthetic and Life Support Drugs Advisory Committee, supplemented by consultants in obstetrics, neonatology, developmental pediatrics, neurology, psychiatry, epidemiology, and biostatistics, recently conducted a comprehensive review of the literature on short- and long-term neurobehavioral effects in infants of drugs used in labor and delivery. The committee concluded that these drugs can exert short-term effects and recommended changes in the labeling of obstetrical anesthetics to include this information. The committee advised that short-term neurobehavioral tests be made mandatory for investigational studies of new drugs—previously it had considered such tests as optional. The committee voted unanimously, however, that no regulatory action was indicated at this time with respect to delayed effects on the child.

When animal and clinical studies on an investigational drug are completed, FDA makes a decision on whether the drug has been shown to be safe and effective and whether its benefits outweigh its risks. For drugs that are specifically indicated during pregnancy, such a decision necessarily involves consideration of risks to the fetus. Drugs for the treatment of premature labor or threatened abortion where evidence showed that they damaged the fetus would not, of course, be approved for marketing.

On the other hand, other drugs which might be used for conditions related to pregnancy or delivery but which would also be used in the general population for other purposes would be approved despite the fact that they may pose a risk to the fetus. In such cases the labeling for these drugs would warn the physician about such risks, and, if they were major, it would recommend that these drugs not be used in pregnant women. For example, the diuretics furosemide and thiazides, used for the treatment of edema—a condition which is not uncommon in pregnancy but which occurs most often in older patients with heart diseases—may cause fetal harm and the labeling for furosemide contraindicates its use in pregnancy except for life-saving conditions and for thiazide warns that use in pregnancy should be judicious. Of course, if a drug that would have wide applicability in a pregnant woman, as well as in the general population, such as a local anesthetic, were to cause serious depression of the neonate in recommended doses, we might very well refuse to approve such a drug for use in labor and delivery because alternatives for these indications are available that do not have this effect.

Benefit/risk considerations are not made by FDA staff alone. We have 15 advisory committees to which important drugs and important new safety issues are brought for deliberation and recommendations for appropriate action. Frequently the committees are aided by consultants with particular knowledge or expertise. Our Fertility and Maternal Health Drugs Advisory Committee, for example, reviewed the new drug applications for ritodrine, a drug used for premature labor, and the drug, bromocriptine, used in female infertility. In both cases safety to the fetus was an important consideration. This same committee also considered the use of oxytocics in elective induction of labor and recommended that such drugs not be used for that purpose.

This committee recently conducted an extensive review of the epidemiologic studies on birth defects in women who received Bendectin for nausea and vomiting of pregnancy. FDA invited world-reknowned experts to appear before the committee in this public meeting. The committee concluded that there is no evidence that a causal relationship exists between Bendectin and birth defects. However, because the committee had a residual uncertainty based on two studies, it recommended continued surveillance. I have previously mentioned the review by our Anesthetic and Life Support Drugs Advisory Committee of drugs used in labor and delivery.

When a decision is made to approve a drug for marketing, FDA takes particular care to assure that the labeling reflects accurately what is known about the safety and effectiveness of the drug, including safety for a fetus exposed to the drug. The labeling is, of course, updated when new risks are identified after marketing.

Labeling for prescription drugs has long contained information on animal reproduction studies, human epidemiologic studies and, when data are available to make such an assessment, whether a drug should or should not be used in pregnancy. For example, labeling for anticonvulsants, minor tranquilizers, certain anti-infective drugs, and cytotoxic anticancer agents contains information on risks to the fetus. In an effort to systematize the information and to provide degrees of relative risk, FDA's new prescription labeling regulations, promulgated in 1979, provide a method for supplying pregnancy information for all drugs in a manner which will allow the physician to make an informed judgment on the advisability of using a specific drug in a pregnant woman and to share the information with the patient.

The prescription drug labeling regulations also provide that, if a drug has a recognized use during labor and delivery (whether or not it is labeled for such use), labeling information must include the effect of the drug on the mother and fetus, on the conduct of labor, and on the later growth and development of the child. If such information is not known, the labeling must so state.

I am submitting a copy of these labeling regulations for the record. All drugs approved in the past 1½ years contain such information in their labeling. For drugs approved prior to 1979, a schedule for relabeling based on drug classes provides for submission to FDA by December 1982 of revisions to their labeling. By 1984 revised labeling for all marketed drugs will be in effect. Many revised labels, of course, will be available to physicians as early as next year. In addition, FDA is developing class labeling for over 30 drug classes. This labeling will enable physicians to compare the risks among the individual drugs in a class. Class labeling has been drafted for narcotic analgesics and anesthetics, drugs which are used in labor and delivery, and these provide information on short-term risks to the fetus and whether or not effects on subsequent growth and development are known.

These labeling efforts will, we believe, go a long way toward providing the best available knowledge in a form useful to physicians and patients. It should be noted, however, that manufacturers are not being asked to conduct animal reproduction studies for old drugs that have never undergone such testing or human epidemiologic studies where such studies have not been conducted before or where conclusions on safety cannot be reached because of the inadequacy of the studies. In cases where data do not exist, the labeling will point out the lack of such information and the physician can judge whether to prescribe a drug whose labeling does not contain information from animal or human studies or to prescribe an alternative drug where information is available.

We are also directing our efforts to a review of the active ingredients in over-the-counter [OTC] drug products for safety and effectiveness and implementation of appropriate labeling. For those drugs for which a potential risk to a fetus has been identified, labels to consumers will contain warning information. Where a drug is used in a prescription as well as an over-the-counter formulation, labeling will be compatible for both formulations. Drugs which are found to pose a serious risk to a fetus will not be permitted to enter or remain on the OTC market.

In addition to labeling, FDA uses other methods to disseminate information on potential risks of drugs. The FDA Drug Bulletin is distributed at least four times a year to over 1 million health professionals. Our magazine, FDA Consumer, has contained articles of interest to pregnant women and reprints are widely circulated to consumers and are available through our district offices and the Consumer Information Center in Pueblo, Colo.

At the time of approval of a new drug for marketing FDA issues a detailed summary of the animal and clinical studies conducted to establish its safety and effectiveness, including adverse effects associated with the drug. These summary bases of approval [SBA's] are available by subscription to all interested parties from the National Technical Information Service.

The drug manufacturers issue "Dear Doctor letters" to disseminate information on important, newly discovered risks. In addition, FDA's drug advertising regulations require that manufacturers provide fair balance in presenting the benefits and risks of their drugs to prescribing physicians.

In your letter of invitation you asked me to consider methods for providing information to patients. As a physician I feel strongly that doctors should inform patients about the drugs they intend to prescribe for them and be prepared to respond to their questions. With respect to written information for patients, many private sources have made such information available in book and leaflet form. As you are aware, FDA requires manufacturers of oral contraceptives, estrogens and progestagens to prepare patient leaflets which contain information on risks of these drugs to the fetus. These leaflets are being distributed by pharmacists.

I am currently reviewing the patient package insert regulation and considering what is the most effective method for assuring that patients receive information about the drugs prescribed for them. Regardless of the method that is found to be most effective, I want to assure you, Mr. Chairman, that whenever a serious hazard is uncovered, such as the risk of estrogens and progestagens to the unborn child, I will require that patients be informed of such risk.

We believe that our current mechanisms for dissemination of information are generally effective but I grant that more might be done to increase information on drug safety. For example, we can also consider use of the television announcements to inform women that drugs may pose a risk to a developing fetus, that they should avoid to the extent possible use of OTC drugs during pregnancy and discuss with their physicians the drugs prescribed for them, including those to be used during labor and delivery. It must be noted that FDA should not bear the full burden of supplying information. The professions of medicine and pharmacy also share a responsibility for providing such information and they have, in fact, assumed this responsibility on many occasions.

FDA uses numerous sources to obtain information on birth defects. A chief source is epidemiologic surveys, such as: The NIH-funded collaborative perinatal study of 50,000 women and their pregnancies, including drug use; the Kaiser-Oakland study of 20,000 pregnant women on which followup data for a subgroup are available for a period of more than 7 years; the ongoing Centers for Disease Control study of trends in birth defects occurring in over 1 million births annually; the case-control studies of birth defects by the CDC and the Boston Drug Epidemiology Unit which assess drug history in mothers of children with birth defects; the Columbia University study of spontaneous abortions on over 7,000 fetuses [most valuable since the majority of birth defects result in spontaneous abortions] and the ongoing analysis of the Seattle-Puget Sound Health Maintenance Organization [HMO] data base of approximately 7,000 pregnancies.

The agency has taken other initiatives to address the problem of drugs in pregnancy, including: The formation of an intramural Maternal-Child Task Force; the conduct of an intensive review of all birth defects and perinatal adverse effects reported to the FDA's adverse reaction system; the coordination of all data sources on birth defects; and the communication to the medical community of our interest in obtaining information on birth defects. These efforts are part of a larger program within FDA of postmarketing surveillance of drugs.

We have established programs which signal problems, such as the spontaneous reporting system, the monthly literature review of over 200 journals for new adverse effects, including birth defects, and specialty registries of adverse effects. We also provide financial support for epidemiologic studies of birth defects and other pregnancy problems which test the hypothesis generated by these signals. These include the Boston Collaborative Drug Study Program, which has used the Seattle-Puget Sound HMO for study of birth defects, the Boston Drug Epidemiology Unit, and the Oxford [England] Survey of Childhood Cancers. In addition, we are beginning to use medicaid data for the study of drug use in pregnancy and birth defects.

These programs have produced valuable information that has resulted in labeling changes, such as those made recently for the drug Bendectin.

Further efforts are desirable and include the following: Greater encouragement of physicians and consumers to report birth defects; expansion of existing intensive local surveillance efforts such as at CDC and the Boston Drug Epidemiology Unit and coupling this, if feasible, with a standard method of documenting drug use in pregnancy; further analysis of existing automated drug diagnosis linkage systems, such as the Seattle-Puget Sound HMO, medicaid, the Collaborative Perinatal Study, and the Kaiser-Oakland data base; development of, or access to, new automated drug diagnosis linkage systems; development and implementation of use of a standardized data record system for all pregnancies and deliveries. Implementation even in a portion of the country and coverage of only a part of the 3 million pregnancies per year would be highly useful.

I would like to make one final comment, Mr. Chairman, because of the nature and importance of the matter, we have given high priority and have devoted a considerable amount of our resources to programs aimed at detecting fetal risk and we intend to continue these efforts. This is not a problem, however, that can be solved by resources alone. Our efforts cannot go beyond the limits imposed by the available methodology to detect such risks and the genuine ethical concerns raised about research in pregnant women.

Mr. Chairman, this concludes my prepared remarks. I would be happy to answer any questions you may have.

Mr. **Gore**. Thank you very much, Doctor, for a thorough statement. We have heard a lot of criticism here today about the risk/benefit process that FDA engages in when approving drugs. While most of us who deal with the FDA on a regular basis know that the drug approval process is a risk/benefit process. I tend to agree with those who say the average American citizen is unaware of this. Particularly when we are dealing with such a sensitive population as pregnant mothers, what can the agency do to make women aware of the kind of process with which we are dealing?

Dr. HAYES. I don't know, Mr. Chairman, except to comment and emphasize and perhaps expand the initiatives we have already taken. The FDA has tried very diligently over the years, in fact, to make physicians aware of what safety and effectiveness mean in terms of drugs and, therefore, of the approval process so they will be aware and can communicate these thoughts to their patients. We have tried through various avenues to reach consumers directly to let them know what we are doing. There are other initiatives with which FDA has been involved or which have occurred independently.

I admit it is a problem and one I must confess I have been concerned about during my post at FDA, that is, on making people aware of what we do at FDA, what some of our problems are, what sort of assessments we have to make in terms of risk and benefit. I would be very happy to receive any suggestions on how to be a better educator; I assure you we are most interested in this.

Mr. GORE. I have a suggestion right off the bat then. The patient package inserts, I think, would be one way to do it. Has the FDA ever, or at least since 1962, not approved a drug because of potential teratogenic effects?

Dr. HAYES. We have not.

Mr. GORE. Now I know that whole classes of drugs are not supposed to be prescribed by doctors to potential mothers, but isn't it true that nothing prohibits the prescribing of DES to women who are pregnant?

Dr. HAYES. There is nothing in the law which the Food and Drug Administration enforces that allows us to tell physicians how to practice medicine. In fact, we have been faulted for trying to do that, though I do not think we were. There is a way, if you will, through the tort system and negligence that physicians are supposed to use drugs appropriately and based on the evidence, but it is not our responsibility and we do not have authority to enforce that, and to tell a physician he may not prescribe a particular drug for a particular patient. We can tell them for what indications we have approved the drug. That is in fact what is in the information insert that accompanies every drug and it is otherwise reproduced or available.

When we say a drug has the following indications, it means that our assessment is in terms of risk and effectiveness and benefit that it may be used for that case but there is no way we can prevent a physician from using another drug.

Mr. GORE. That is my understanding, too. But what I am getting at is if you then find a pattern of abuse, that the lack of that option ought to enhance your willingness to take more action against the availability of the drug itself.

Dr. HAYES. The problem is that very often these drugs, such as DES, are used in situations where there is no substitute or, at least, in many patients there is not. DES is used in intractable forms of cancer. If we took that off the market because a physician could use it inappropriately, we would deprive other patients that would feel we had no right to keep it from them.

Mr. **GORE**. Do you have indication that DES is still being prescribed in inappropriate circumstances?

Dr. **HAYES**. I do not have any positive data. If you ask me do I think that it ever occurs, I cannot believe it does not, but I have no evidence that it does.

Mr. **GORE**. Dr. Finkel, do you have such reports?

Dr. **FINKEL**. I have seen a draft of a study made on use of DES, and other estrogens, and oral contraceptives for postcoital use. The paper is not published. Actually the study showed that DES is used very uncommonly. This was a study done on students. In fact, the most common drug use for postcoital contraception was an oral contraceptive.

Mr. **GORE**. Is it true, Dr. Hayes, that if thalidomide were going through the new drug evaluation process today, there is a good chance that it would be approved?

Dr. **HAYES**. I cannot speak to that because I do not know what tests it would have gone through. When we saw it, it was a compound that came from another country. So there is no way for me to assess, in 1981, what studies it would have been subjected to.

Mr. **GORE**. Well, let's say that it was introduced in this country today and the American consumer relied not upon what other countries did but what its own Food and Drug Administration did to protect the American public. Isn't it true that there is a good chance that thalidomide would make it through the new drug evaluation process at the FDA today?

Dr. **HAYES**. You mean in terms of reproductive studies or just in general? Because in fact, the compound was not approved because of a problem that FDA assessed in terms of peripheral nerve damage that was found in the countdown.

Mr. **GORE**. What really happened, as I understand it, was that you had some good luck over there—some good work but also some good luck—and also it laid around for quite a long time during which time reports of serious malformations from countries around the world began to come in, and that focused the attention of the FDA on the specific drug thalidomide.

Dr. **HAYES**. That is right. There is no question that the evidence on the phocomelia came from other countries. The reason it was lying around the FDA is because of an adverse effect, or toxicologic effect about which we were concerned. So there was reason for our not approving the drug. There is no question that had that not occurred and had reproduction studies and others not shown any problems, then the drug might very well have been approved. But it is a little difficult in hindsight to know what information you would have had.

It is not a question so much of relying on information but we are sensitive to any information about a drug, wherever it is obtained. We will assess the data to see if we think the data are valid, but it is not a question of relying upon it. We look for any data or information and track it down, if we think it relates to the approval of the drug or to the use of the drug once it has been approved.

Mr. **GORE**. Well, in the ongoing debate over streamlining the procedures, a goal which I, too, want to see reached by FDA, it is well to keep in mind the risks which are still very grave. I know that you require reproductive toxicity tests to be performed, but isn't it true that under your own criteria you might disregard a positive test for a teratogen?

Dr. **Hayes**. I do not understand what you mean by disregard. If you mean that because a drug is positive in a test that there is no way it can get on the market, that is not true, because you might deny people that would not be at that risk, such as postmenopausal women, infertile women and certainly half the population which is male and certainly those for whom the use of what might be a very valuable drug. I would not say we disregard it, it becomes a very important part of the approval process and certainly of the labeling.

Mr. **Gore**. The FDA guidelines as I understand them indicate that a positive test for teratogenicity is not necessarily a reason to disapprove a drug. Now I understand that the state of the art might be such that positive teratology might not be dispositive. But it strikes me we need to be more candid with the American people about what we know and what we do not know with respect to this.

Dr. **Hayes**. As I pointed out in my testimony, Mr. Chairman, this information will be in the labeling or the fact that we do not have the information will be there. It is true that the guidelines do not demand or call for absolute refusal to approve a drug because there is a positive teratogenic study in animals. Indeed, for an indication that a drug be or could only be used and indicated through labeling for use in prostatic cancer, it would not make any difference. What is important is to make people aware, and we think that the labeling which we have updated and think is current with the state of science today will make this information available.

Mr. **Gore**. Mr. Shamansky?

Mr. **Shamansky**. Doctor, of necessity, the system here makes it difficult to have perfect continuity, although the chairman is trying to achieve that as much as possible.

If I may continue: I know that Mrs. Haire has tried and now our subcommittee staff has tried to get a list from the FDA of those drugs that are specifically indicated and specifically contraindicated for use in pregnancy and that your agency cannot generate this kind of a list. Don't you believe that publication and circulation of this kind of information would be extremely helpful, if not crucial, in giving people important information on which to make their choices?

Dr. **Hayes**. Well, I think it could be helpful but I am not at all sure it is necessary. I am not saying——

Mr. **Shamansky**. Let's just take helpful. I am assuming your agency wants to be helpful if nothing else; correct?

Dr. **Hayes**. That is right.

Mr. **Shamansky**. Are you going to get such a list, and how long would it take to get it?

Dr. **Hayes**. I do not know. It would be expensive, very expensive indeed.

Mr. **Shamansky**. Why would it be so expensive?

Dr. **Hayes**. Because the system is not geared. With all the drugs that are variable and all the information the system is not geared, and it would be rather expensive from the standpoint of resources to so teach the system, if you will, to pull out all drugs by indications and by contraindications.

Mr. SHAMANSKY. That is going to be—the prospective cost is such in your mind that you would not make a list——

Dr. HAYES. No, I did not say I would not, but I would have to consider what it would cost me to do it.

Mr. SHAMANSKY. At what point do you think it would be too expensive?

Dr. HAYES. I do not know. I can not make that assessment.

Mr. SHAMANSKY. You say you don't have any criteria as yet as to what would be too expensive?

Dr. HAYES. No, I do not. Understand it is possible to know for any drug whether in fact it is indicated or contraindicated in pregnancy by merely looking at the information on the drug.

Mr. SHAMANSKY. Yes. Assuming that the inquirer knows all about every drug, supposing he wants—the physician is inquiring as to what any number drugs might be good or bad available at his particular location. In your method he is limited strictly to what he may know at the moment.

Dr. HAYES. No. All he has to do is look at the information that is available on every drug. If he is looking for a diuretic for a particular condition, he merely has to look at the information on each of the two, three, four available diuretics. Under the new labeling this will be even easier, because for the important groups of drugs we will have class labeling whereby merely looking at the information for a drug you will know the comparative assessment for all of the drugs in that class. We have addressed that problem, and I think the class labeling will go a long way toward solving it.

Mr. SHAMANSKY. I know you are about to complete regulations on drug labeling that will categorize drugs A through X—A, B, C, D, and X, concerning what we know about their effects on a fetus. Of course, I think your agency is to be commended for that. Isn't it also true under the system a category A drug that is supposed to be safe for use during pregnancy can be designated without either short or long-term followup clinical studies or epidemiological studies after a drug has been approved? We really don't do anything in a systematic way to followup drugs that might have problems at the moment, do we?

Dr. HAYES. If I understand your question on category A drugs where human studies have in fact been negative, then we do not demand that every such drug, those that would be relatively safest, have the epidemiologic or surveillance studies. What you are suggesting is that we have to have surveillance on every approved drug, because this would be the one with the less predictive risk.

Mr. SHAMANSKY. Let me ask you, do you have any system, criteria, program for following up any drugs except in the most haphazard of fashions?

Dr. HAYES. No, that is not true at all. We have a number of studies for surveillance of drugs just as we have had postmarketing surveillance of drugs in the past. It is not possible, we feel, to do this for every drug or indeed some drugs would never get to market if it were necessary. What we try to do is determine by the studies we have, for example, for category A drugs, where we have epidemiologic data by definition we try to make a determination whether further epidemiologic studies or long-term surveillance will be really helpful.

Mr. **SHAMANSKY**. Doctor, on page 5 of your prepared statement you have the sentence:

> For drugs other than those used for a condition related to pregnancy, FDA's clinical guidelines advise that pregnancy tests be performed prior to introduction of an investigational drug in women of childbearing potential.

What do you mean by advise? Is that the equivalent of require?

Dr. **HAYES**. Guidelines are advisory, that is what we think the clinical investigator should do and should require in his study or before the conduct of the study.

Mr. **SHAMANSKY**. And it would be satisfactory to you or to the field in general if they just ignore the advice?

Dr. **HAYES**. I think if they ignore the advice we would be concerned, perhaps, about their competence to perform that sort of study.

Mr. **SHAMANSKY**. Then why not require them?

Dr. **HAYES**. Because it is very difficult to tell physicians or require what they are going to do. All we really have in terms of enforcement is that if they do not do certain things that we think are scientifically or ethically justified or their IRB, institutional review board, feels that you should not let them do the studies.

Mr. **SHAMANSKY**. It seems to me implicit in your statement is the fact that it would be bad, it would be unacceptable if they didn't, so there is pressure on——

Dr. **HAYES**. There is pressure on them to do it. There are exceptions that one can conceive—perhaps a bad verb—but perhaps it would not be appropriate in a particular study. I do not think it is possible to make a generalization that we never have to have it, it is a very clear and emphasized part of the guidelines that this should be part of the protocol.

I might point out that we do not always have the final judgment, that is to say, institutional review boards can be rather more strict about some of these guidelines as well.

Mr. **SHAMANSKY**. On page 6 of your prepared statement you say the majority of the drugs cannot be assessed for field safety in clinical trials prior to marketing.

Are you satisfied with that condition?

Dr. **HAYES**. No, I am not satisfied at all. I wish that the state-of-the-art would allow us to have adequate and realistically predictive prescreening and screening and definitive studies, so that we knew as much as we could, including teratogenic effects for every drug.

Mr. **SHAMANSKY**. Mr. Walgren?

Mr. **WALGREN**. Thank you, Mr. Chairman.

I wanted to touch on a couple of subjects, particularly with respect to Bendectin. First, this, as I understand it, is the warning that goes to physicians along with the drug, which may or may not be passed on to the consumer. Without objection I would ask that that be submitted in the record at this point.

Mr. **SHAMANSKY**. Without objection.

[The information follows:]

Bendectin

DESCRIPTION

Each specially coated tablet contains:

Decapryn® (doxylamine succinate)—antihistamine	10 mg.
Pyridoxine hydrochloride	10 mg.

ACTIONS

Bendectin provides the action of 2 unrelated compounds. Doxylamine succinate, an antihistamine, provides anti-nauseant and anti-emetic activity; the pyridoxine hydrochloride provides vitamin B_6 supplementation to help avoid pyridoxine deficiency that may occur during pregnancy. Also, studies indicate B_6 has an anti-nauseant activity. The anti-emetic action of Bendectin is delayed by a special coating that permits the nighttime dose to be effective in the morning hours—when the patient needs it most.

INDICATION

Bendectin is indicated only for nausea and vomiting of pregnancy which are unresponsive to conservative measures such as eating soda crackers or drinking hot and cold liquids, which interfere with normal eating habits or daily activities, and are sufficiently distressing to require drug intervention. (See Precautions—Pregnancy.)

PRECAUTIONS

Because of potential drowsiness, Bendectin should be prescribed with caution for patients who must drive automobiles or operate machinery.

Pregnancy: Studies in rats and rabbits have revealed no suggestion of drug-induced fetal abnormalities at doses of Bendectin up to 90 times the maximum human dose. A review of eight cohort epidemiologic studies (i.e., those which compare a group of individuals exposed to a risk factor with a non-exposed group) in women who received Bendectin during pregnancy and five case control studies (i.e., those which seek to detect a specific birth defect) leads to the conclusion that the existing data do not demonstrate an association between Bendectin usage and birth defects. However, two the case control studies sugested the possibility of an increased risk of a certain type of defect, cleft lip/palate in one study and heart defects in the other. Because these two results emerged after multiple analysis of the same data (i.e., looking at many drugs) and for other reasons, these findings are viewed at this time as hypotheses and not as definitive findings. Other studies did not report an increased risk of these defects, but additional studies are ongoing to help clarify the matter. The design of the cohort studies was generally adequate to have detected a small increase (less than a doubling[1]) in the overall malformation rate, if it existed, but was not sufficient to rule out a doubling of a specific malformation type, for example, 1 per 1000 to 2 per 1000. For the above reasons, Bendectin should be used only when clearly needed for the treatment of nausea and vomiting of pregnancy not responsive to conservative (non-drug) measures.

When a decision has been made to use drug therapy in the treatment of nausea and vomiting of pregnancy, the physician should be aware that Bendectin has been the subject of a considerably larger number of epidemiologic studies searching for a risk of birth defects than have other antinauseants.

ADVERSE REACTIONS

The adverse reactions that may occur are those of the individual ingredients. Doxylamine succinate may cause drowsiness, vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, or irritability.

Pyridoxine hydrochloride is a vitamin that is generally recognized as having no adverse effects.

DOSAGE AND ADMINISTRATION

[illegible] Bendectin tablets at bedtime. In severe cases or when nausea occurs during the day: 1 additional Bendectin tablet in the morning and another in midafternoon.

---

[1] Doubling is the level of sensitivity many epidemiologists regard as feasible to detect in the design of studies of this type.

HOW SUPPLIED

Bottles of 100.

Mr. **WALGREN**. I don't have any cross-examination on that to do except to indicate for the record that it is a very complex statement, one that is sort of beyond the understanding of the average individual, if it were to wind up in their hands, and try to underscore the point that whatever is done in communicating these kinds of reservations or facts about a drug be attempted to be put in the most understandable form. I am sure that that is consistent with what you had outlined earlier in your intent; is that correct?

Dr. **HAYES**. That is right, and I think there is a point to be made here. That information is designed and written for physicians, who do not want to be talked down to, who want all the information. If it is complex, they feel they are capable of dealing with it and then make a judgment. Bendectin, in this circumstance, is complex in terms of the risks, relative benefits and the like. There is no question in the PPI program, the patient package insert that is available as part of that program when it is implemented in whatever form is written in lay language and is quite different from the material you have before you.

The audiences are different and just as the patient doesn't want to read a medical journal, the physician does not want to read a newspaper.

Mr. **SHAMANSKY**. Will the gentleman yield?

Am I to infer from that statement that you have a program for PPI?

Dr. **HAYES**. There was a program for PPI's proposed and put in the regulations before I became Commissioner 3½ months ago. When I became Commissioner, I was told I would be responsible for this study and for the interpretation of this, a test study as it was designed. My concern was that I was not sure it was the best study and I wanted, since I would be responsible for its implementation and analysis and further decisions, to be sure about the study. The study is on hold, if you will, until I have finished my assessment this summer of the program and whether in fact I believe it is a good study and whether it will answer the questions: That is, do the patients get the information, do they understand it, is it the best, the most effective, the most cost-effective way to do it, and does it result in some change? Does something happen in terms of decreased adverse effects, decrease in inappropriate use of drugs, decreased interaction of drugs and the like?

Mr. **SHAMANSKY**. You have said a lot in words, but what are you driving at, Doctor? Are you saying that you are not going to use simple language to tell the patient what the effects will be?

Dr. **HAYES**. No, not at all. What I am saying is that this particular program, the patient package inserts for 10 drugs was designed as a study. That after 2 years it would be determined whether this was a good way to do it, cost effective, educationally effective and the like. I did not design it.

Mr. **SHAMANSKY**. If I may suggest, the testimony of every witness today—I can't think of an exception—has said it would not be very helpful.

Dr. **HAYES**. That the package inserts——

Mr. **Shamansky**. Yes, in layman's language, that would be helpful.

Dr. **Hayes**. Well, there is a great difference of opinion as to whether PPI's would be helpful.

Mr. **Shamansky**. Where does the opposition to PPIs' helpfulness come from?

Dr. **Hayes**. There are many——

Mr. **Shamansky**. I would be interested in the idea that it would be not helpful.

Dr. **Hayes**. Many physicians feel it is an intrusion upon their practice; they are responsible for educating patients and they do not think a piece of paper which is uniform for all patients for a particular drug or group of drugs given by a pharmacist or stuck in a package is appropriate.

Mr. **Shamansky**. And we were discussing Bendectin, do you apply that to Bendectin?

Dr. **Hayes**. That is why I am reviewing the program. One of the questions is: Is it a good study to see if it is an effective method? Part of that question has got to be answered by that to the further question for what drugs are PPI's appropriate. There are thousands of drugs. Should there be PPI's for all drugs, or, if not, for which drugs and for which drugs can we best determine the efficacy?

Mr. **Shamansky**. Then you are saying that the objection is a philosophical one on the part of physicians as to whether or not they control the education of the consumer but the consumer, the one who gets the drug administered to her and she has a child, under this philosophy she is not to be given that privilege?

Dr. **Hayes**. There are many who feel it is the physician's responsibility to give that information. I am not saying I subscribe to that.

Mr. **Shamansky**. How do you feel?

Dr. **Hayes**. I think physicians should provide the information, I think frequently they do not.

Mr. **Shamansky**. They should provide it? But what happens if the physician chooses not to, how do you feel about the consumer's right to get the information.

Dr. **Hayes**. I think the consumer has a right to know about their drugs.

Mr. **Shamansky**. How do you feel about a patient package insert?

Dr. **Hayes**. I do not know if that is the best way to do it.

Mr. **Shamansky**. When do you think you will know?

Dr. **Hayes**. I will know this fall.

Mr. **Shamansky**. This fall?

Dr. **Hayes**. I will know this fall how to do the study to find out if it works. There are no data to find out if this is an effective means.

Mr. **Shamansky**. The reason I am stressing this is that clearly based on Mrs. Haire's work it would be kind of integral. I wish to assure you that every one of the witnesses uniformly thrust far up until you felt PPI's would be something that would be helpful. Do you believe a patient has the right to know about possible adverse effect?

Dr. **Hayes**. I do, with some exceptions, I think there are some cases where it is not appropriate to tell a patient.

Mr. **Shamansky**. OK. Where in the Hippocratic oath is the doctor given the right to filter the data?

Dr. **Hayes**. No, I am not suggesting the physician has the right to filter data.

Mr. **Shamansky**. Isn't that the inevitable result of this philosophy that it is the doctor who has the right to educate the patient?

Dr. **Hayes**. No. I am saying the doctor has the responsibility to educate the patient. If he does not do it or doesn't do it properly, then we have to find other ways to do it.

Mr. **Shamansky**. It seems to me what you are doing is saying the doctor makes a choice but he doesn't suffer the consequences.

Dr. **Hayes**. That is correct. I am not saying that the patient does not have the right to get the information.

Mr. **Shamansky**. How are you going to get the information to him?

Dr. **Hayes**. I do not know, that is what I am trying to find out; I am trying to find out the best way; I am trying to design a study to find the answer to that question. PPIs are not the only means of providing patient information that have been tested.

Mr. **Shamansky**. I didn't mean to suggest it was the only method. To this legislator it seems one rather direct, simple method.

Dr. **Hayes**. Well, it is direct if in fact the patient will read it. It is not simple, it is extremely complicated and expensive, that is the problem.

Mr. **Shamansky**. Simple in the sense that it is with the medicine at the point of contact with the person who is going to consume it, simple in that sense. I didn't mean to suggest that the information contained is simple, it could be very complex information. I am talking about a method of informing a consumer about something that will affect that consumer's life and that of her child. I am not sure whether your doubt is about the desirability of the information getting to the consumer or merely the technical aspects of this study.

Dr. **Hayes**. Of the methodolgy.

Mr. **Shamansky**. Pardon?

Dr. **Hayes**. The methodology of providing that information.

Mr. **Shamansky**. And that is a big problem for you.

Dr. **Hayes**. Yes, it is a very big problem indeed. There is no use embarking upon a program unless you are going to know at the end of the study whether the results mean anything. If we put, merely, PPIs or any other system of patient education out there and at the end of two, three, five years, we do not know if it has made any difference, then why do we go to the effort or how do we decide between the various modes of providing the information?

Mr. **Shamansky**. Doctor, it is my understanding that your two predecessors believed in the efficacy, the desirability of having patient package inserts. Do you agree with them in that assessment?

Dr. **Hayes**. I do not know, and I do not know for which drugs. I am not sure they are necessary for every drug that is on the market, if indeed that could be workable. For every pharmacy to have thousands of package inserts I think would be difficult. What perhaps we ought to do if patient package inserts are the most effective way to provide this information, is also decide for what drugs they are most important, drugs with highest risk or drugs in high risk groups.

Mr. **Shamansky**. We have been concentrating here on pregnant women. How about for that class of consumers?

Dr. **Hayes**. You ca not very well, I do not think, design a system of information whether patient package inserts or something else for a class of patients, it has to go with the drugs. Because pregnant women for one reason or another take a variety of drugs, perhaps more than they should, but they still take them nevertheless or at least the possibility exists that they could be prescribed for them.

Mr. **Shamansky**. I guess my difficulty and candor requires me to say that apparently it is good for the patient to have the information, but there is something about the idea of the patient package insert that seems to have great difficulty for you.

Dr. **Hayes**. No, there is nothing about it that has difficulty for me. I am just not sure how to find out whether it is the best way to provide this information or if in fact it is worth the effort.

Mr. **Shamansky**. Worth the effort? Using what criteria to decide worth the effort?

Dr. **Hayes**. I do not know, that is what we are trying to do.

Mr. **Gore**. Will the gentleman yield?

The fact of the matter is that—let's be candid about it—it has been studied for a large number of years and those who have studied it from the viewpoint of the public have come to the conclusion that of course it is possible for patients to be given this information in this form but the pharmaceutical industry has chosen upon the transition to the new Administration and their contacts to flex their muscles and bring the process to a grinding halt. I mean that is really what has happened, isn't it, in all candor?

Dr. **Hayes**. Well, it has not to me because I have not talked to anybody in industry about patient package inserts since I have been here and my ideas about patient package inserts were chiefly formulated before I became commissioner. At that time nobody seemed to care what I felt.

Mr. **Gore**. Your ideas about patient package inserts as they have been expressed here are that you don't know? What are your ideas about patient package inserts?

Dr. **Hayes**. I think patient package inserts should be studied to see if in fact that is a reasonable and effective way of providing necessary patient information, and further, for which drugs or in what form should they be made available. To say I am against patient package inserts is absolutely untrue, and I have never made that statement; I do not think it can be inferred from anything I have said. The FDA patient package insert program was designed to be a study.

Mr. **Gore**. Do you recognize a commitment made by FDA to prepare or require a patient package insert for Bendectin?

Dr. **Hayes**. Yes, that was one of the drugs in the group in the pilot study, that is correct.

Mr. **Gore**. Have you withdrawn that commitment?

Dr. **Hayes**. I have not withdrawn that commitment.

Mr. **Gore**. Does the commitment still stand?

Dr. **Hayes**. It does. The whole program has been stayed.

Mr. **Gore**. Why?

Dr. **Hayes**. Because I do not know whether that is an appropriate drug and I do not know if that is an appropriate way to provide the best information about Bendectin.

Mr. **Gore**. Isn't it true that the industry has fought PPI's in every forum and at every step along the way? And isn't it also true that in speeches during the transition period spokesmen for the industry indicated that the stopping of patient package inserts was part of their agenda and that they were predicted that the patient package inserts announced in the previous Administration would not be for the coming——

Dr. **Hayes**. I can not speak to whether they predicted that, and as far as public statements from the groups that we have discussed here, and I serve to be corrected, the Pharmaceutical Manufacturers Association, I believe, in open testimony before a committee of the U.S. Congress said that they thought that some form of patient package insert was probably inevitable and probably a good thing. I know that in open testimony the American Medical Association said they were categorically against them.

Mr. **Walgren**. Will the gentleman yield?

I was particularly pleased to hear you say that you certainly honor the commitment to implement a patient package insert with respect to Bendectin because it is my understanding that that commitment did not come from the patient package insert program or the push for the patient package insert from any consumer groups but rather was one of the balancing vehicles that the FDA's own committee on fertility and maternal health drugs would be very appropriate for Bendectin because of the uncertainties involved and the fact that you are dealing with a pregnancy which involves another human being rather than just the person who is taking the drug. The Bendectin PPI, it seems to me, stands on a very different ground it seems to me than do the patient package inserts that might be recommended for other drugs, at least as to the FDA's commitment to them. That is why I was very disappointed when all were put on hold. I would really like to ask that you look at Bendectin, in particular, and the patient package insert with respect to Bendectin differently than you do the other 10 that were agreed to.

Dr. **Hayes**. I think that is a very good point. I think what happened temporarily is that the interest in having a patient package insert on this compound occurred at about the same time as this pilot program and therefore it seemed reasonable to do the one with the other. I think that makes sense. If good data on the effectiveness could be obtained, you would have it on a very important drug and one that the advisory committee was concerned about.

If for some reason, and I cannot state it now, but if for some reason the patient package insert test program would not for scientific reasons include Bendectin, then we would have to make a very important decision. Should not a PPI be done, as it is now for estrogens and progesterones and oral contraceptives, on its own merits? That is a very good point. The reason the two came together was fortuitous on a temporal basis. I think the dichotomy would open up again depending upon the form of the decision.

Mr. **Gore**. How long will it take for the FDA to decide whether or not patient package inserts ought to be issued for Bendectin? Do you have an estimate?

Dr. **Hayes**. It is going to take a couple of months because, as you know, there are administrative procedures that when I examine anything in terms of policy meetings, and comment periods and the like are necessary. And I am not a lawyer. I am sure Mr. Scarlett could answer the details of this if you like. I can tell you it will be done with all the dispatch possible, because I think the whole area of patient education and education in medicine and pharmacology, which I have been interested in since I finished medical school, is a very important one. I would not want you or the subcommittee to think that I am not interested in patient education. I have been involved in this a long time.

The question before me is, Is this a good study? Is this a good way for me to find out if this is the most effective way to educate the public in general about drugs through patient package inserts. I am going to be held responsible for that study when it is finished. Therefore it is my obligation, I feel, to be sure it is a good study. There is no scientist that I know of worth his or her salt that will conduct somebody else's study and then be held responsible for it.

Mr. **Shamansky**. I was very pleased to learn just now that you have thought for a long time about patient education. Drawing upon that long experience as an educator, what do you know now as the most efficacious way of informing the consumer, the patient, as to the effectiveness of drugs and its effect on her, in this particular case, and the child? You don't come here totally uninformed.

Dr. **Hayes**. I hope not. I think the best and most efficient way is an individualized and thorough and explicit discussion of the drug by the physician who is prescribing it.

Mr. **Shamansky**. That does not change anything that we have now, does it, basically?

Dr. **Hayes**. I am not sure how often that occurs.

Mr. **Shamansky**. Let me say that this is pretty clearly all we have been doing so far, relying solely upon whatever the physician does. The question we are raising with you here today is, How can we go beyond, without in any way prohibiting the physician from doing that? Why do we continue a reliance on the one method which has already proved it is not doing the job?

Dr. **Hayes**. It is not doing the job totally in many cases.

Mr. **Shamansky**. This is what we are talking about, the totally part.

Mr. **Gore**. If the gentleman will yield.

We had testimony today from Dr. Brackbill that demonstrated quite clearly, it is not a matter of whether the information is totally getting there, pregnant women in this country don't have any idea what the effects of drugs prescribed and taken during pregnancy are. They just don't know. She did a very thorough study. There have been other studies. Pregnant women in this country are not aware of the effects on the fetus of the drugs that they take during pregnancy. And contrary to a statement in your testimony which I think was phrased slightly differently, we had other testimony that more drugs are being consumed during pregnancy today than ever before, and not only are pregnant women not getting the information but the labels are actually misleading them into believing erroneously that the drugs have been looked at for the effect on fetuses and have been given the green light for that purpose. And here we have a proposal that worked up—that has been worked up over a long period of time to give a communication directly to the patient taking a drug, explaining what the risks and benefits are, and how they are compared, and it is held up. And I think that—well, it is obvious what I think about it; I think you ought to go forward.

Mr. Walgren?

Mr. **Walgren.** I would just like to underscore the point that the FDA, at least last year, was in the position of relying on the Fertility and Maternal Health Drug Advisory Committee's recommendations and that was the ground that they stood on to be assured themselves that they were not putting the public to an undue risk. So when you turn to that committee's recommendations, you find it immediately asking for a patient package insert with respect to Bendectin and no other drugs at that point. And I hope you would evaluate that on that basis, because the FDA—and I know the public is relying on the FDA, and the FDA is relying on the experts, and the experts now say that because of the particular uncertainties involved with this drug and its relationship to pregnancy that a patient package insert would be especially appropriate and in fact recommended.

And I think part of that may be because we have women in tremendous amounts taking Bendectin, 23 percent; when you go in and you ask the experts how many do you think should be taking Bendectin and they say it should be reserved for the extremely rare cases, obviously there is an excess use of the drug. I think the committee, between the lines, was knowing if they put this information in the hands of women a number of them would be conservative enough in their own approach to their pregnancy that you would cut down on that excess use that we all know is there.

Dr. **Hayes.** I think that is what they were clearly implying and I think that was the hope of their recommendation.

Mr. **Walgren.** Let me go on to another subject. I would like to try to understand for the record how the FDA develops information on adverse reactions, adverse experiences in the community.

Now we have a system for collecting adverse drug problems, do we not? How does that happen?

Dr. **Hayes.** With your permission I am going to ask Dr. Jones, who runs the office responsible for that, to give you better information than I can.

Dr. **Jones.** Basically the adverse reaction drug experience program begins at the time the drug is approved for marketing. And it extends in four areas, actually. One is the one which has been discussed today, that is the reports from the manufacturers. Manufacturers are required presently to report to us all adverse reactions reported to them. If they are severe, and that includes birth defects, they have to be reported within 15 days; otherwise, they are reported in periodic reports quarterly, biannually and annually. That is the first source, and it is the major source at the present time.

Mr. WALGREN. Major source is the manufacturer?

Dr. JONES. Of spontaneous reports, yes. The second source is directly from the medical community. That accounts for about 15 percent of our reports. And those are retrieved by soliciting reports, usually through the drug bulletin.

The third source is from the medical literature. As was noted in the testimony, we survey 200 English-speaking journals on a monthly basis and capture all information about new and suspected adverse effects and also include this in our surveillance.

The fourth area is from specialty registries. We currently support four specialty registries which collect adverse reactions including hepatic reactions, eye reactions, et cetera. These adverse reactions are collected and considered as signals of problems. They are reviewed on a weekly basis, and we categorize them into a series of priority levels. Those of highest priority are those which are not on the label and are considered serious. We use corroborating information, including information from the other spontaneous report sources, as well as our other funded contracts, to determine whether or not this should be carried further.

Mr. WALGREN. So it is your evaluation of the reports that you receive that focuses the efforts and the attention of the agency.

Dr. JONES. That is probably the primary system. It is fair to say that we are also cognizant of reports that we should be finding; that is, on a new molecular entity that is on the market or might be used in pregnant women that otherwise was not studied. We are somewhat on the alert for this type of reaction, whether we get it or not.

Mr. WALGREN. But your primary source for that, or certainly a major source for that would be from the manufacturer? He, of course, is the place that the person who is surprised by an experience would go first and ask, I gather, and it is very important that you receive those reports that the manufacturer becomes aware of?

Dr. JONES. Yes, that is correct. And, some of these inquiries come in as inquiries rather than strict reports. We are cognizant of that dilemma and currently have revised our reporting form for the industry and also are developing guidelines to clarify that.

Mr. WALGREN. Why is that a dilemma, something coming in as an inquiry.

Dr. JONES. Sometimes it comes in as a question, have there been any cases of such and such?

Mr. WALGREN. Would the law require the manufacturer to report that? Would the law require the manufacturer to report to the FDA an instance where the manufacturer become aware of someone's belief that an adverse reaction was experienced?

Dr. JONES. The regulations require that if the manufacturer is aware of an adverse experience they are required to report that to us.

Mr. WALGREN. I am curious as to the difference between an inquiry and their being aware of an experience and whether or not we are losing reports because they may be treated as inquiries by the manufacturer but not knowledge of experience that is required to be reported to the FDA?

Dr. **Jones**. Congressman, we are concerned about the same thing, which is why we are currently making very specific guidelines with respect to that specific issue, which will essentially request that an inquiry be followed up by a request for information, if an experience, in fact, is the basis of that inquiry.

Dr. **Hayes**. A word, if I may, Congressman, on this one because you put your finger on one of the biggest problems in all of clinical medicine and clinical pharmacology, that is when is a drug-induced adverse reaction really a drug-induced adverse reaction? One of the biggest problems we had in hospitals for years, and still have on that side of it as a clinical investigator and a hospital clinical pharmacologist, was being sure on the one hand that some truly drug-induced adverse reactions went unreported, the very thing you are talking at a different level in terms of the inquiry rather than the adverse reaction report.

Equally a problem in terms of any meaningful analysis and subsequent action is that every time somebody thinks there might be an adverse reaction or something changes in a complex individual or somebody thinks that maybe something could happen, that it is put down as a positive adverse drug reaction, because on that basis one could be afraid to use a drug or to use it in patients because of all the adverse reactions, and they are not really there. And in any hospital, any hospital clinical pharmacologist will tell you this, the hardest thing is not to get people to write something down, it is to write down something they are rather sure about or that they have checked on in a patient. To put down that somebody developed a headache after they took a particular drug is no help in assessing the headache potential of that drug unless you find out if the patient has a brain tumor, hypertension or is taking six other drugs. And that is a very real problem that you put your finger on and it goes both ways, and there is no way to presume that they cancel out.

Mr. **Walgren**. At this point in the record, without objection I would like to introduce a copy of a letter that was from Lucy Buckley at Children's Hospital that I believe the committee does have a copy of already. I think it goes right to this point where the manufacturer was made aware—and this has to do with Bendectin—the manufacturer was made aware of a study in which the conductor of the study felt there was an extremely high incidence or certainly it raised great question about whether or not Bendectin was related to the cardiac malformations, as I understand it, that were discovered in this study. Yet I am positive that was never reported to the FDA even though it involved some 1,000 incidences of heart defects related in this, or raised the question of whether in fact some 1,000 heart defects were related to Bendectin. And this letter in my view was carefully written by a lawyer in the company to throw the ball back to the person doing the study in a way that legally there was no obligation to report this to the FDA. Certainly the FDA was never informed of it.

[The information follows:]

PHYSICIAN'S SIDE EFFECT REPORT

1. Product BENDECTIN
Date started NA
Control number NA

2. Daily dose
Overdose: Amount/Frequency 1 DAY
Length of treatment with drug before adverse effect first noted NA
NA

3. Patient's initials
Sex Weight NA
Date of birth; Mo. Day Year

4. Race:
☐ Caucasian NA ☐ Negro ☐ Oriental
☐ American Indian ☐ Other

5. Specific indication for which drug was prescribed:

NAUSEA IN PREGNANCY

6. Adverse reaction(s): Date of onset of reaction: Mo. Day Year
Describe:
CHILDRENS HOSPITAL MEDICAL CENTER CARDIOLOGISTS HAVE NOTED BENDECTIN INGESTION IN MOST CONGENITAL HEART DISEASE PATIENTS' PRENATAL HISTORY. WILL YOU CHECK WITH OTHER PEDIATR CARDIOLOGISTS?

7. Interval between last dose and onset of reaction:
☐ Concurrent
☐ Within 1 hour MOS - YEARS
☐ Over 1 hour but within 12 hours
☐ Over 12 hours. Specify

8. Severity of reaction:
☐ Severe
☐ Moderate NA
☐ Mild
Duration of reaction:

9. Was drug discontinued?
If yes, give date NA
If drug continued, give dose

10. Was drug reintroduced?
If yes, give date NA
Did adverse reaction reappear?

11. Were any laboratory tests made? ☐ Yes ☐ No If yes, describe:

12. Concomitant therapy:
Drug name USUAL DOSE VITAMINS IRON Dates

13. Has the patient been exposed to the suspected drug before?
If yes, was there an adverse reaction at that time? NA

14. Were there other disorders present before or just prior to the onset of this reaction? ☐ Yes ☑ No
If yes, describe:

15. Has the patient been exposed to any toxic agents before or just prior to this reaction? ☐ Yes ☑ No
If yes, describe:

16. Has this case been reported to any other group or agency or submitted for journal publication? ☐ FDA ☐ AMA
☐ Other manufacturer ☐ Other ☐ Literature: Journal reference

17. Side Effect reported by: (Please Print) ROBERT L. SHIRLEY Date 27-MAY-77
Signature Robert L Shirley MD Telephone No. 617-734-5387
Street 33 POND AVE
City BROOKLINE State MASS Zip Code 02146
Merrell Representative Territory No

DEC [illegible] 1977

Lucy Buckley, M.D.
Department of Pediatrics
Children's Hospital
300 Longwood Avenue
Boston, MA 02115

Dear Doctor Buckley:

Re: Bendectin

This letter is in follow up of our phone discussion of June 17, 1977.

A Physician's Side Effect Report (PSER) form has been received from Robert L. Shirley, M.D., by way of Merrell-National representative, Terry Chester. This form was dated May 27, 1977 and received here on June 6, 1977.

I then called Dr. Shirley on June 15, 1977. In the original form submitted by him, he had entered the following statement: "Childrens Hospital Medical Center cardiologists have noted Bendectin ingestion in most congenital heart disease patients' prenatal history. Will you check with other pediatric cardiologists."

In my follow up phone call of June 15, 1977, however, Dr. Shirley informed me that he had meant the sheet coming to us as being an inquiry and not a report of a problem. He had asked, as stated in the above quote, that we ask elsewhere. In the conversation, he identified you as the source of his information, and I was left with the impression in my discussion with Dr. Shirley that he thought that nearly every patient with a heart problem had a mother who took Bendectin. I informed Dr. Shirley that I would be following through with you as soon as possible. I, therefore, appreciate your returning my call on June 17, 1977 after my attempts to try to locate you on June 16, 1977.

You kindly informed me on June 17, 1977 that you had on record over 3,000 pediatric patients with severe cardiac problems. Your records had started in 1968. You were working off the records of the pediatric patient. You had not been to the mother's history. It was your impression, but you could not quote figures during our phone call, that less than 1/3 of the patients had mothers that had received Bendectin. You, however, needed time to pursue such percentage of mothers who took Bendectin before making a final statement.

FILMED FROM
BEST COPY AVAILABLE

You were, in fact, only now beginning to evaluate records, and this included medication of the mother as stated on the child's history.

You also confirmed that the entire communication involving the indirect report from you by way of Dr. Shirley, my phone discussion with Dr. Shirley, and my phone discussion with you of June 17, 1977, be handled as an inquiry at this point in time. We shall, therefore, remove the PSER form dated May 27, 1977 by Dr. Shirley from the Drug Experience Report category. If at a later time it should be returned to the category, it will be so done. When so returned, information will be supplied to the U.S. Food and Drug Administration.

I referred you to Allen A. Mitchell, M.D. of the Pediatric's Department of your Hospital in that he would be available at extension 2930. I mentioned him to you because he is a collaborator on the 1977 book entitled: Birth Defects and Drugs in Pregnancy authored by O. P. Heinonen, D. Slone, and S. Shapiro, Publishing Sciences Group, Inc., Littleton, Massachusetts. You had not seen this book, but wished to have the appropriate reference so that you could locate it.

Bendectin has been available as a three-ingredient product for about two decades up to November, 1976. Since November, 1976, it has been commercially available as a two-ingredient product. It now contains doxylamine and pyridoxine (see attached file card). The formula also contained dicyclomine hydrochloride. It was removed with FDA concurrence from this combination after additional testing showed lack of statistical clinical efficacy over that already contributed by the doxylamine and pyridoxine by the study protocol used. I have attached another letter of today's date which summarizes results of the efficacy study and to which a summary report is attached.

It is understood that you will phone me (collect), if in your further review and collation of data, find a correlation of cardiac problem and ingestion of Bendectin by mothers. Furthermore, I hope you will feel free to call me if I may be of any help in such efforts. I will be happy to visit you in Boston if you deem that this could be of aid.

On the basis of information available to us, we see no correlation of Bendectin ingestion by mothers and the incidence of anomalies of their offspring. We see no evidence of an increase of anomalies of offspring of mothers who received Bendectin over that in the general population or of women who did not receive Bendectin. I refer you especially to the book by Heinonen et al. and the copies of papers attached to the accompanying letter.

FILMED FROM
BEST COPY AVAILABLE

Much of the above is a summary of the phone discussion with you. If any portion needs to be edited, please do so, return to me, and a photocopy will be sent to you.

Your returning my call on June 17, 1977 is indeed appreciated, and I shall await further comment from you before additional action is taken.

Sincerely yours,

Dorsey E. Holtkamp, Ph.D.
Group Director
Endocrine Clinical Research

DEH:deg

Enclosures

cc: Allen A. Mitchell, M.D.
Epidemiology Unit
Children's Hospital
300 Longwood Avenue
Boston, MA 02115

Robert L. Shirley, M.D.
33 Pond Avenue
Brookline, MA 02146

FILMED FROM
BEST COPY AVAILABLE

Mr. **Walgren**. Are you aware of this letter, Dr. Jones?

Dr. **Jones**. I just became aware of it about 3 to 6 months ago but that was the first time we became aware of it. It was subsequent to our study of the Bendectin defects.

Mr. **Walgren**. But the letter was written in June of 1977 so it has been several years without the FDA having knowledge of that. Is the information in that letter the kind of information that you feel the FDA is required to have by law?

Dr. **Jones**. Well, this is something that Dr. Hayes has just addressed. It is a dilemma because—a dilemma further emphasized by Dr. Slone's testimony, the reporting of an event which is temporarily associated with a drug does not necessarily mean that there is any causal relationship. So there is a great deal of ambiguity all the way from the observer, that is the physician, on through the chain as to whether there is a causality inference. We have chosen to say we would rather make the causality decision because we basically have a process by which we look at drugs and events in an agnostic fashion and then try to make some inference.

Mr. **Walgren**. Given the fact there is a great deal of ambiguity the question then arises as to who is the proper one to resolve that ambiguity? Would you agree that certainly the manufacturer is not the one to resolve that ambiguity?

Dr. **Jones**. We made a general policy to request the manufacturer to report all experiences to us in the precise language, recognizing this ambiguity issue. Making the point of decision at the FDA rather than the manufacturer.

Mr. **Walgren**. How long has that policy been in effect?

Dr. **Jones**. Since I have been there, for 3 years approximately.

Mr. **Walgren**. Three years?

Dr. **Jones**. I think that has been a general policy prior to my coming.

Mr. **Walgren**. Then the question arises as to whether the FDA has the ability to go out and see whether that policy is being enforced or not, or followed, rather, and it would seem to me that when we have an agent, that is, the manufacturer, who we all know is not the person that we would put this burden on, then there must be some independent look at the question of whether all proper reports are in fact being forwarded to the FDA? Certainly we would do that where there is a substantial amount of controversy or smoke. Would that be your feeling, Dr. Hayes?

Dr. **Hayes**. I think it is very important that we get the information. The question is how in fact does one get it, police it, enforce it? How does one know where to look? I quite honestly do not think most manufacturers have warehouses full of hidden information. I think, on the other hand, there is no question that every event that ought to be reported for our judgment is in fact so reported. I think it is somewhere in the middle.

But I do not have any quick answers. I certainly do not have adequate resources to go out and start digging for every possible event, either at the level of the manufacturer or at the level of doctor-patient or hospital-patient interaction.

Mr. **Gore**. If the gentleman will yield. Do you think you need more resources to evaluate that information?

Dr. **Hayes**. Not to evaluate the information when it comes; I do not know. If it turned out that there was a lot that we had not seen, then that might be very true. I cannot give you any suggestion on what resources or increased resources would be needed to go find that information.

Mr. **Gore**. But you do think you need more.

Dr. **Hayes**. Well, you would need more if you increased it because there is only so many things that could be done.

Mr. **Gore**. Do you think you need to increase it?

Dr. **Hayes**. I am not sure—I think it has to be increased, I don't know by what magnitude.

Mr. **Gore**. Then why did you cut this item in the budget from $1.5 to $1.1 million.

Dr. **Hayes**. Because we do not have any authority now to go out and dig the information. We are talking now about extramural work that is used for developing information and assessing it and making decisions based upon it.

Mr. **Gore**. This is the extramural research budget item, isn't it?

Dr. **Hayes**. That is right. But an extramural budget is not the same, if you will, as a force of detectives or a whole new system to go out and see where the information is or to go to hospitals and set up whole complete adverse reaction reporting systems. I can tell you nobody to this date outside the Government, let alone inside the Government, has found an adequate adverse drug reaction reporting system. And some very intelligent and experienced people have tried.

Mr. **Gore**. Well, it would make sense to do some more work, then, to try to develop that, wouldn't it?

Dr. **Hayes**. I think it would be delightful.

Mr. **Gore**. Why are you cutting the budget in that category?

Dr. **Hayes**. Because I have only so much money; and as the money stays the same and the job gets bigger, I have to decide where to put it.

Mr. **Gore**. Why don't you reallocate it from some other area then?

Dr. **Hayes**. Because I am afraid those concerned about those areas would ask me why I had done it. The priorities and distribution of money has to be made, and when there is relatively less money for the same or even an expanding job, one has to make decisions. If you have to cut all around, I am afraid that is the realities of the situation.

Mr. **Walgren**. Will the gentleman yield?

Mr. **Gore**. Yes. You have the time.

Mr. **Walgren**. I certainly know that there isn't any way that we can examine every manufacturer, but would it make sense where we are investing a great deal of effort, even the convening of special councils of experts to look into a specific drug, that the FDA make a particular onsite evaluation of whether or not, in fact, you have all the data you expect to have on any given drug? In this instance, we are not talking about 50 manufacturers, I am sure. This instance is just a way I would like to, as a consumer, know that the FDA was taking the individual initiatives so that I knew the Government wasn't being sort of—I don't know what the word would be—led astray or not fully informed where it really counts. Wouldn't it be appropriate, regardless of what your budget is, that when you have an issue that you are investing aggregate deal of resources in and it is a very important and broadly used question, in this instance Bendectin, that you make a specific evaluation of whether you have received all the necessary data that you expect from the drug manufacturer?

Dr. **Hayes**. I think that is very true, and I think in specific cases we not only can do it, but in fact we have done it. In fact, there was some concern because of physicians' spontaneous reporting on liver toxicities with a diuretic drug that was marked a couple of years ago—the generic name is ticrynafen—because we had concerns about this, the timeliness of reporting, adequacy, so on, we in fact did what you are suggesting. So it can be done. The mechanisms are there. I think we are not quarreling at all about whether it is a good thing. It is a question of deciding on which drugs and at what stage you go out and do it. I couldn't agree with you more.

Mr. **Walgren**. I would just like to draw your attention to, in particular, Bendectin in this instance. There may be others, but I know about this particular drug and I know that Dr. Jones, at least, has had the benefit of evaluating this letter that raises the direct question. There are other reports that we feel were not forwarded to the FDA that would, I think, direct your attention even more toward Bendectin. So I would like to encourage you to follow through on that approach.

Dr. **Hayes**. I appreciate that Congressman.

Mr. **Walgren**. Thank you.

Mr. **Gore**. Dr. Jones, do you think the company violated the guidelines that would require them to report such a communication to the FDA?

Dr. **Jones**. I haven't looked at this communication for several months. My recollection of the communication, direct communication, would suggest that—I don't want to directly answer that without looking at that communication. The communication was in the form of an inquiry. My understanding is that the company interpreted that as such and did not interpret it as a drug experience report. Had we known of that we would have considered that a drug experience report.

Mr. **Gore**. You know, there are 770,000 pregnant women in the United States who take this drug every single year. There is no good epidemiological study that can answer the questions about it that we know about, and we are refusing to, for the time being at least, to tell American women directly that there is a risk associated with it and we are relying on the company to report instances of adverse effects.

Here a doctor writes about numerous cases and—let me see—the company says, you are wrong, don't worry about that, this is no big deal. The regulations supposedly require the company to inform FDA about reports of this kind. FDA finds out about it, nothing is done. Nothing is done. Did you make any inquiries of the general counsel, for example, as to whether or not the regulations might have been violated by their withholding of this adverse report?

Dr. **Jones**. Our interpretation was that that report—the interpretation of the current regulations and reading of the current regulations is such that an inquiry could be construed as an inquiry and not a drug experience. We have currently taken steps to rectify that. That is our current approach, recognizing that type of ambiguity shouldn't occur.

Mr. **Gore**. OK. With your indulgence, I am going to recess for a few minutes. There is a vote on the floor. Then we will try to wrap up as quickly as possible.

Mr. Shamansky is on his way back over here and he will crank it up.

[Recess.]

Mr. **Shamansky**. Moving right along, Dr. Hayes. I was hoping Mr. Scarlett was here. I am sure he will be back.

The reason I was hoping that Mr. Scarlett would be here, maybe he can advise you on it: I remain somehow or other skeptical, if not incredulous, about the apparent inability except beyond reasonable cause to prepare a list of drugs that would affect the fetuses of pregnant women. And I am just—I cannot see, I cannot imagine a court or the House of Representatives, itself, denying or overturning a subpena from, say, this subcommittee and committee, to the Food and Drug Administration seeking that information.

Dr. **Hayes**. You mean just a list of all the drugs that have an indication in pregnancy? Or contraindications?

Mr. **Shamansky**. A couple of the witnesses today have said they have sought what they thought was reasonable, and it struck me as reasonable, and obviously I have the tremendous disadvantage of not being the director of the Food and Drug Administration as you do. You have that great responsibility. But at some point or another each of us has to say, gee, what sounds sensible, what sounds reasonable? And it didn't occur to me, still doesn't, I hate to tell you, occur to me that with some reasonable effort that such a list couldn't be determined.

Dr. **Hayes**. Such a list could be determined, Congressman, for that as well as for 100 other areas; drugs that are a problem in pediatrics or interact with another. We have been asked for such lists or parts of such lists for various indications and contraindications and warnings and the like. If I had the facilities and the staff, one could program a computer and put this information in and bring the information out in many different ways. If there is significant interest and a realistic expectation that a list of all the drugs that have been indicated in pregnancy and those that have been contraindicated—that is, something that is positive data—if there is sufficient indication and expectation of its use, then the list can be generated. I am not sure doing it through the computer would be the most cost effective way. It might be better to sit down with a PDR and just go through it page by page with a pencil.

Mr. **Shamansky**. If you notice, I didn't suggest that the computer was involved or not involved. Ultimately someone tells the computer what to do, so I think you start with people. Since we are honored to have you here today it was logical to start with you.

The reason I am responding in the way I am is my hope that the medical profession, and I am including you and your agency in that, the health professions, can achieve a lot more by cooperating than getting the feeling as if they were with an adversary position. I, frankly, Doctor, am uncomfortable with the idea that the public feels, the concerned part of the public feels that they have to turn to the Federal Government for assistance here. My theme has been consistently today what is the medical profession doing on its own, academic medicine, organized medicine, and I would hope that that is the kind of a thing that could be done voluntarily, with sort of an outgoing open attitude on the part of your agency, which is apparently a key element in this cooperative venture that I like to think we are following.

Dr. **Hayes**. I could not agree more, and I hope that there is not. Or, if there is, that we can resolve any adversarial or arm's length relationship between the Food and Drug Administration and the medical profession. Quite obviously as a physician-Commissioner it makes me something a little less than schizophrenic. I think it is important that we work together. There is clearly enough work to be done and there are some very real problems, and the best way to do it——

Mr. **Shamansky**. I hope, just my own personal hope that the whole question of the information with the Food and Drug Administration has, par excellence, certainly more than any other entity in the country, with respect to the effect of drugs on children, on fetuses and their mothers, that your agency could do its best in that area.

Dr. **Hayes**. I appreciate your concern, Congressman, we certainly will.

Mr. **Shamansky**. Doctor, throughout our investigation, it has become clear that one of the major problems in dealing adequately with the effects of drugs in pregnancy is the lack of adequately predictive animal data, the lack of teratology. I know that your agency is investing some money, at the National Center for Toxicological Research and through the national toxicology program testing chemicals and developing methodology. I wonder if you would tell us what drugs you currently are testing within NTP and why they are being tested, and what additional drugs you would like to see tested?

Dr. **Hayes**. At this stage, Congressman, it is not a question of drugs, it is a question really more of chemicals, not necessarily those used for human drugs. This is a methodological search and evaluation right now. I would be happy to give you a list of the compound being tested. Some of these are in fact drugs that are used in humans. I would be happy to mention them if you like.

Chlorpromazine hydrochloride is one. Hydrochlorothiazine, a diuretic is another. Oxytetracycline, which is a broad spectrum antibiotic; probenecid, which is used in certain problems such as gouty arthritis; sulfamethazine, which is a sulfa drug; and caffeine, which is found in a number of over-the-counter analgesic preparations. That is not an exhaustive list. Some others are being used because chemically we hope they will bring some benefit in the methodology.

Mr. **Gore**. We are going to have two additional votes in a row. We would like to submit some additional questions for the record, Doctor, and in the remaining 7 minutes or so try to ask some more.

At the time I left for the last vote, Dr. Jones, I was asking about the apparent withholding of data from the FDA by this company. Would you agree that they have withheld data on alleged adversary actions, Bendectin, which should have been reported to FDA.

Dr. **Jones**. As I said, our current understanding of what we would like now, that would be the type of information we would like. I would say at the time we received it was after we had done a fairly thorough look at all of the epidemiologic studies on Bendectin at the time. So we were able to address this. This is a very general letter. Also, the patients involved in it were part of a study which is one of the epidemiologic studies that addressed it. So we were already aware of the issue by the time we received it.

Mr. **Gore**. Dr. Hayes, some of the labels on drugs approved by FDA appear to be quite misleading to pregnant women. They say, for example, that this medication should not be used—is not approved for pregnancy except during labor, and the implication is that it has been examined for use during labor and that risks have been assessed, quantified, and evaluated and that the patient is being told that the risks are acceptable, when in fact the FDA has no idea what the risks are.

Dr. **Hayes**. I do not think that is quite true that we do not know what the risks are. It is just that it is a different circumstance. If you are talking about using a drug in labor where there may be a specific medical indication for its use at some other time when the risk/benefit would be quite different since the indication would be quite different. I am not suggesting that all of our labeling for physicians, which is the labeling I believe you are referring to——

Mr. **Gore**. Yes——

Dr. **Hayes** [continuing]. Is as clear as it might be and could not be improved. We attempt to do this all the time. I think what is meant there seems to be reasonably clear because labor is a different circumstance than other uses for such a drug.

Mr. **Gore**. But the indication is that it has been specifically approved for that purpose.

Dr. **Hayes**. Indeed the drug may in fact be approved for that purpose. Perhaps I misunderstand your question, Mr. Chairman.

Mr. **Gore**. What drugs are approved for that purpose?

Dr. **Hayes**. Which purpose are you speaking of?

Mr. **Gore**. For use during labor.

Dr. **Hayes**. There are a number of drugs. Certain local anesthetics are used during labor.

Mr. **Gore**. No, no, no. Which are approved by FDA for use during labor?

Dr. **Hayes**. That is what I am addressing.

Mr. **Gore**. Go ahead. Can you supply that for the record?

Dr. **Hayes**. Surely.

[The information follows:]

Mr. **Gore**. Under what conditions do you believe it is appropriate and necessary for the agency to ask industry to undertake followup epidemiological studies? For example, let's take the drug Ritodrine, the labor-delaying drug. We heard testimony this morning from an eminent obstetrician from Johns Hopkins who believes that the risk/benefit ratio on this drug may be fairly narrow, to say the least. I understand that you have started some followup epidemiology on this drug and that you were tracking it carefully.

What other drugs currently on the market have this kind of risk/benefit posture and what would you have to find before you pulled a drug like Ritodrine off the market?

Dr. **Hayes**. I think before we pulled a drug like this off the market there would have to be sufficient data to suggest that it was a drug that should not be used in terms of benefit because of the risks that had been demonstrated. This drug is used for a very specific indication, and that is to prevent premature labor. Clearly, if this drug was shown in a surveillance or epidemiologic study or evaluation that it damaged the fetus, then it wouldn't make very much sense to use it to prevent premature—spontaneous or premature labor in spontaneous abortions. So the kind of drug is important. This particular drug is the only one indicated or approved for that specific indication. So one cannot generalize about drugs for different indications or to be used for different reasons.

Mr. **Gore**. Yes. Under what circumstance would you consider asking the industry to undertake followup epidemiological studies as a condition of approval? You are cutting the budget for your own epidemiology. You say the need is there and you ought to have more information but you are simultaneously cutting the resources necessary for that purpose. You say the patient ought to have more information, but you put a hold on the only ongoing effort that would provide the patient with more information.

Under what circumstances would you consider asking the industry, which after all makes lots and lots of money on the sale of this stuff, to undertake—not only to comply with the regulation itself on reporting adverse experiences but to affirmatively undertake followup epidemiology?

Dr. **Hayes**. I think probably in terms of priority it would be those drugs that we believe would be used for a prolonged period during pregnancy, because the best evidence is, and I think it is also fairly logical in a predictive way, that these are the drugs that would be most likely to cause long-term effects if indeed they caused them at all, rather than one that is used literally for five minutes or four hours at the time of labor or at the time of delivery. Clearly——

Mr. **Gore**. Now on what basis do you cull out the neurotoxic effects and assume they have no real cause for concern?

Dr. **Hayes**. You mean acute neurotoxic effects?

Mr. **Gore**. Long-term neurotoxic effects.

Dr. **Hayes**. It is not a question of saying they don't mean anything. I was responding to your question as to what sorts of drugs would you schedule for long-term testing.

Mr. **Gore**. Yes.

Dr. **Hayes**. I think the criteria, at least for priorities, it would be nice to do it in terms of everything, but I think in terms of priority criteria, those that are used for a prolonged period during pregnancy and especially those that have a wide use. Now what data you got from such surveillance or epidemiologic studies would then have to be analyzed by the best methods available. I don't think you would cull out any neurotoxic data. If you saw neurotoxicity, then you would use your best epidemiologic and statistical weapons to see if you really thought it had been caused by the drug. As we heard Dr. Slone say today, that is not easy, but there are methods such as his case method where this could be done.

Mr. **Gore**. OK. I appreciate your willingness to come today and to answer other questions for the record. We intend to pursue this matter.

Mr. **Walgren**. Would the gentleman allow one further short pursuit—one further question?

Mr. **Gore**. Very quickly.

Mr. **Walgren**. Dr. Hayes, we talked about the possibility of inquiries that the FDA would want to have forwarded on to the FDA that might not be by manufacturers.

It is my understanding that the frequency of this is quite high with respect to Bendectin. It is also my understanding that the company keeps a docket of all the initial receipts of experiences, but then not all of them are forwarded on to the FDA because some are treated as inquiries and others are not treated as inquiries and those would be forwarded on.

Now the FDA has been operating under a policy, as I understand the testimony of Dr. Jones, for several years where even inquiries are to be forwarded to the FDA. Is that correct, Dr. Jones?

Dr. **Jones**. Our hope is that is the case, yes.

Mr. **Walgren**. Yes. Now my request is that the FDA compare the logbook that is kept by the manufacturer of this particular drug with your recorded FDA adverse experience reports. It is a very simple, one-trip ministerial function, perhaps; could be done very conveniently, to see whether that policy, that you have stated to the committee has existed for this period of time, has been followed in this case. I would sleep much better, I am sure pregnant women would sleep much better knowing that was in fact the case. Could you help me with that particular?

Dr. **Hayes**. I will do my best and see what authority and what possibilities there are. But as you pose it, it certainly seems like a reasonable comparison.

Mr. **Walgren**. Thank you.

Mr. **Gore**. Thank you. Thank you all for coming here today. I must say I have been impressed that Mrs. Haire and Dr. Brackbill were the only two witnesses today who seemed to perceive an urgency in the use of drugs during pregnancy. Our other witnesses have all shared two characteristics; they lack that sense of urgency and some see little problem. I am not a scientist and can't evaluate the evidence to determine accurately the degree of risk involved, but all witnesses here agree that there is some risk. I must say that I am greatly concerned at the lack of empathy. I believe we must do more. I will continue to pursue this issue to see that the public is given the benefit of the doubt rather than the other participants involved.

I would like to thank you again for participating in the hearing, and we will stand adjourned.

[Whereupon, at 5:38 p.m., the subcommittee was adjourned.]

○